



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 October 2025
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIBTAYO

International non-proprietary name: Cemiplimab

Procedure No. EMA/VR/0000264999

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ALK	Anaplastic lymphoma kinase
C _{avg ss}	Average concentration at steady state
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
C _{max}	Maximum concentration
C _{max,ss}	Maximum concentration at steady state
CSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
C _{trough}	Trough concentration
C _{trough,ss}	Trough concentration at steady state
DCO	Data cutoff
DFS	Disease-free survival
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EDM	Epidermotropic metastases
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-3L	EuroQoL 5 Dimensions 3 Levels
FAS	Full analysis set
FFDR	Freedom from distant recurrence
FFLRR	Freedom from locoregional recurrence
FU	Follow-up
GHS	Global health status
HN	Head and neck
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim Analysis
IHC	Immunohistochemistry
ITM	In-transit metastases
IV	Intravenous

LRR	Locoregional recurrence
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death receptor-1
PD-L1	Programmed death-ligand 1
PNI	Perineural invasion
PRO	Patient-reported outcomes
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	C-ROS oncogene 1 receptor tyrosine kinase
ROW	Rest of world
RT	Radiation therapy
SAP	Statistical Analysis Plan
SD	Standard deviation
SPT	Second primary CSCC tumor
TPS	Tumor proportion score
TROG	Trans-Tasman Radiation Oncology Group
US	United States
UV	Ultraviolet
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Regeneron Ireland Designated Activity Company submitted to the European Medicines Agency on 07 April 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include adjuvant treatment of adult patients with Cutaneous Squamous Cell Carcinoma (CSCC) at high risk of recurrence after surgery and radiation for LIBTAYO, based on interim results from study R2810-ONC-1788; this is a phase 3, randomized, placebo-controlled, double-blind study of adjuvant cemiplimab versus placebo after surgery and radiation therapy in patients with high risk CSCC; As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the warnings for the excipients proline and polysorbate to reflect EU guidance (Section 4.4), and also updated Annex IID of the PI in line with the updates made to the RMPv4.2 to consolidate the aRMMs.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0414/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was completed.

The PDCO issued an opinion on compliance for the PIP P/0414/2023.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 28 February 2019 (EMA/H/SA/3225/6/2018/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The appointed CHMP Rapporteur was: Boje Kvorning Pires Ehmsen

Timetable	Actual dates
Submission date	7 April 2025
Start of procedure:	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on:	20 June 2025
PRAC Rapporteur's preliminary assessment report circulated on:	24 June 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2025
MAH's responses submitted to the CHMP on:	12 August 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	16 September 2025
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	19 September 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	7 October 2025
CHMP opinion:	16 October 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The proposed new indication is: *Libtayo (cemiplimab) as monotherapy is indicated for the adjuvant treatment of adult patients with CSCC at high risk of recurrence after surgery and radiation.*

Epidemiology and risk factors

CSCC is one of the most common cancer in the white populations, accounting for 20% of all cutaneous malignancies (Stratigos et al., 2020: <https://doi.org/10.1016/j.ejca.2020.01.007>). The incidence varies according to geographic region with the highest incidence in regions closer to the equator. The exact incidence is unknown due to underreporting of cases in the cancer registers. For example, among western European countries, the annual age-standardized incidence is estimated to be 6.9 cases per 100,000 people; while, in Australia and New Zealand, the annual age-standardized incidence is 249.7 per 100,000 people (Guo, 2023). The reported incidence of CSCC has steadily increased in recent decades in many geographic regions (Guo, 2023) (Olsen, 2024) (Tokez, 2020).

The likelihood of developing CSCC is dependent upon exposure to risk factors (most importantly ultraviolet light) and patient-specific characteristics, such as older age, immunosuppression (organ transplant recipients, CLL), skin type and genetic predisposition (i.e. xeroderma pigmentosa) (UpToDate).

Clinical presentation, diagnosis and stage/prognosis

The clinical presentation of CSCC varies depending on tumor size, differentiation, pigmentation, location and skin type. The most common location are sun-exposed areas, such as the head, neck, upper limbs, and the backs of the hands. In an early stage, the lesions are usually a small flesh-coloured plaque or papule, sometimes with a scaly/hyperkeratotic surface. CSCC can be pigmented, presenting a light to dark brown colour. Well-differentiated CSCCs are typically hyperkeratotic and verrucous tumors, sometimes more or less crateriform. Poorly differentiated CSCCs appear as red fleshy non-keratotic tumors with frequent ulceration (Stratigos et al., 2020). Overall, CSCC has a low potential for metastasis, typically spreading first to regional lymph nodes and then to distant sites. The estimated rate of metastasis is between 2% and 5%. Despite this low metastasis potential, distant metastasis is linked to a poor prognosis, with a median survival of less than two years (Stratigos et al., 2020).

According to the 2022 NCCN guidelines CSCC can be classified as being at very-high and high-risk of recurrence, metastasis or death if any of the clinicopathological features are present:

- Tumors of any size located on the head, neck, hands, feet, pretibia, and genitalia
- Tumors 2 to 4 cm on the trunk or extremities (excluding hands, feet, pretibia)
- Tumors >4 cm on any location (very high risk)
- Recurrent tumors
- Certain histopathologic subtypes (acantholytic/adenoid, adenosquamous, metaplastic)
- Tumors >6 mm in thickness
- Tumors with perineural, lymphatic, or vascular invasion

The 2022 NCCN risk stratification for CSCC was found to be clinically significant in predicting poor outcomes. In a study of 8,727 patients with 10,196 tumors, high-risk and very high-risk tumors had a 2- and 13-fold higher risk of local recurrence (subhazard ratio [SHR] 1.99, 95% CI 1.21-3.27; and SHR 12.66, 95% CI 7.86-20.39, respectively) compared to low-risk tumors, even after adjusting for age, sex, and surgical method (Stevens et al, 2022).

The risk of recurrence (local, regional and distant) for high-risk CSCC is highest within **the first three years** after primary treatment (Win et al, 2023; <https://doi.org/10.1016/j.jaad.2022.11.035>).

Management

The majority of early stage CSCCs are curable with the local therapy (surgery, radiation therapy, photodynamic therapy and other local therapies). For invasive lesions, surgery, with either Mohs micrographic surgery (MMS) or wide local excision (WLE), is the treatment of choice. The cure rate of CSCC managed by surgery is approximately 95% (Breuninger, 2013). The 2023 European Association of Dermato-Oncology (EADO; Stratigos et al. 2023; DOI: 10.1016/j.ejca.2023.113252) proposed treatment algorithm for patients with CSCC is as follows:

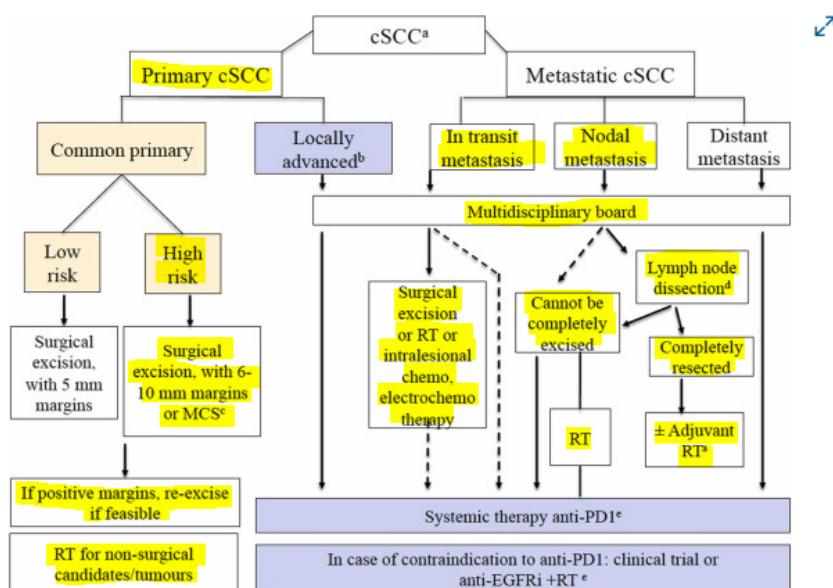


Figure viewer

Fig. 1 Proposed treatment algorithm for patients with cSCC. Strength of consensus: 90%. ^aFor detailed indications and recommendations of treatment, refer to the relevant section text in the Guidelines. ^bLocally advanced by definition not amenable to curative surgery or RT. ^cMicrographically controlled surgery instead of sectional assessment is advised, when available. ^dLymph node dissection as indicated. ^eIn Europe, all systemic treatments are off-label, except for the anti-PD-1 agent cemiplimab that is approved by EMA for patients with locally advanced or metastatic cSCC who are not candidates for curative surgery or curative radiotherapy. cSCC, cutaneous squamous cell carcinoma; MCS, micrographically controlled surgery; RT, radiotherapy.

Patients with locoregional recurrence not amenable for rescue with surgery or RT or patients with distant metastasis constitute a therapeutic challenge. The only approved treatment for this population in the EU is cemiplimab.

For patients at high risk of CSCC recurrence after curative intent local modality treatment, there are no approved adjuvant treatment options. The TROG 05.01 trial (Porceddu, 2018) also known as "POST," investigated the effectiveness of adjuvant radiation therapy (RT) alone versus adjuvant RT combined with concurrent carboplatin in patients with cutaneous squamous cell carcinoma (CSCC) who had undergone complete surgical resection and had specific clinico-pathologic features. The primary aim was to determine freedom from locoregional recurrence (FFLRR). The study concluded that there was no statistically significant or clinically meaningful difference in FFLRR between the two treatment groups.

Therefore, there is an unmet medical need for an effective treatment option with an acceptable safety profile in patients at a high-risk of CSCC recurrence after radical surgery and post-operative RT to maintain the cure achieved with local therapies and prevent disease recurrence.

2.1.2. About the product

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.

The currently approved indications for Libtayo are:

- as monotherapy 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
- as monotherapy for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).
- as monotherapy for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in $\geq 50\%$ tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:
 - o locally advanced NSCLC who are not candidates for definitive chemoradiation, or
 - o metastatic NSCLC.
- in combination with platinum-based chemotherapy for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in $\geq 1\%$ of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:
 - o locally advanced NSCLC who are not candidates for definitive chemoradiation, or
 - o metastatic NSCLC.
- as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

The new indication is:

LIBTAYO as monotherapy is indicated for the adjuvant treatment of adult patients with CSCC at high risk of recurrence after surgery and radiation (see section 5.1 for selection criteria).

The recommended dose of cemiplimab administered as an intravenous infusion over 30 minutes is:

- 350 mg every 3 weeks for 12 weeks followed by 700 mg every 6 weeks, or
- 350 mg every 3 weeks.

Treatment may be continued until disease recurrence, unacceptable toxicity, or up to 48 weeks of total therapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

During the SA given by the CHMP in 2019, the CHMP agreed with the proposed inclusion criteria, stratification factors, crossover and collection of PROs during the study. Some recommendations were proposed by the CHMP concerning DFS and addition of histological grade as stratification factor for pre-planned subgroup and multivariate analyses. The main issue pointed out by the CHMP was that the MAH planned to perform a time-depend DFS analysis with a prespecified number of events, which would not inform about curability of the disease but delay in relapse. Fixed-time endpoint analysis

when the risk of relapse is expected to be low in both arms (around three years) was recommended, as the goal of therapy in this setting is to increase cure rate and it would be expected that nearly 50% study population would never relapse after radical primary local treatment. This would lead to exposing some patients to unnecessary risk of toxicity without any potential benefit. The CHMP stressed that if the MAH would continue with the proposed event-driven analysis of DFS/EFS and would not demonstrate increase in DFS at the time, where the risk of relapse curves is expected to reach plateau in both groups (i.e. 3 years according to the natural history of disease), there would be an uncertainty about positive B/R in this population as the delay in DFS for patients with residual disease would have to be weighed against the risk of toxicity for patients, who might not have benefit from the treatment. Additionally, the CHMP recommended sensitivity analysis in case new SCC would not be counted as event in DFS analysis since it is common that new SCC will develop in the majority of the target population. The MAH maintained their proposed methodology, which includes an event-driven DFS approach, incorporation of the initially proposed stratification factors, and the exclusion of new SCC lesions as events in the DFS analysis.

2.1.4. General comments on compliance with GCP

The MAH states that the study 1788 was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences, International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and other applicable laws and regulations.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Cemiplimab is a monoclonal antibody consisting of naturally occurring amino acids. According to section 4 of the 2024 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline) (1), due to the physico-chemical nature of cemiplimab's active substance, this product is unlikely to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Study Identifier/ Location of Study Report/Synopsis Study Status/ Type of Report	Objective(s) of the Study	Study Design and Type of Control and Duration of Treatment	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects/ Patients	Diagnosis of Subjects/ Patients
R2810-ONC-1788 (Phase 3 Clinical Study in Patients with High-risk CSCC) Study Ongoing Primary Analysis CSR	Primary Objective: To compare DFS of patients with high-risk CSCC treated with adjuvant cemiplimab, vs those treated with placebo, after surgery and RT. Secondary Objectives - To compare the OS of high-risk CSCC patients treated with adjuvant cemiplimab, vs those treated with placebo, after surgery and RT. - To compare the effect of adjuvant cemiplimab with that of placebo on patients' FFLRR after surgery and RT. - To compare the effect of adjuvant cemiplimab with that of placebo on patients' FFDR after surgery and RT. - To compare the effect of adjuvant cemiplimab with that of placebo on the cumulative incidence of SPTs after surgery and RT. - To evaluate the safety of adjuvant cemiplimab and that of placebo in high-risk CSCC patients after surgery and RT. - To assess cemiplimab PK and immunogenicity in human serum.	An ongoing randomized, placebo-controlled, double-blind, phase 3 study of cemiplimab as adjuvant treatment of patients at high risk of disease recurrence after resection of CSCC The study consisted of 2 parts Part 1 (blinded): Part 1 of the study constitutes a screening period of up to 28 days prior to randomization, a treatment period of up to 48 weeks, and a follow-up period. Patients undergo post-treatment follow-up until disease recurrence or end of study. Part 2 (unblinded): Optional cemiplimab treatment, for up to 96 weeks, is allowed for patients on the placebo arm who experience disease recurrence. Optional subsequent	cemiplimab: 350 mg q3w for 48 weeks or Cemiplimab 350 mg q3w for 12 weeks followed by 700 mg q6w for 36 weeks (starting amendment 2) or placebo.	415 patients were randomized (209 patients to cemiplimab arm and 206 patients to placebo arm)	Patients with high-risk of CSCC recurrence

Study Identifier/ Location of Study Report/Synopsis Study Status/ Type of Report	Objective(s) of the Study	Study Design and Type of Control and Duration of Treatment	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects/ Patients	Diagnosis of Subjects/ Patients
		treatment with cemiplimab, for up to 96 weeks, is allowed for patients on the cemiplimab arm who experience disease recurrence ≥ 3 months after completing 48 weeks of planned cemiplimab treatment In Part 1, patients were randomized equally to one of the following 2 arms: • Cemiplimab monotherapy • Placebo			

2.3.2. Pharmacokinetics

Bioanalytical methods

Pharmacokinetics

Cemiplimab in serum samples from the 1788 study was quantified using the validated ELISA method utilized in the initial MAA, see EPAR: EMA/CHMP/368468/2019. The LLOQ of the bioanalytical method is 78 ng/mL in human serum.

Immunogenicity

Anti-drug-antibodies (ADA's) were detected using the previously validated bridging immunoassay. The sensitivity of the assay in serum is approximately 2.4 ng/mL of the monoclonal mAb positive control (REGN3461). The drug tolerance in serum is approximately 415 µg/mL of cemiplimab in presence of 100 ng/mL REGN3461. The titer was determined for confirmed positive ADAs. No NAb analysis was conducted.

Pharmacokinetic data analysis

Nonlinear mixed effects modeling methodology was implemented using NONMEM (version 7.5.0) software. The FOCEI method was utilized. Pre- and post-processing of data from each modeling step and graphical analysis of the data was performed using R (version 4.2.2).

Evaluation and qualification of models

Pop PK modelling

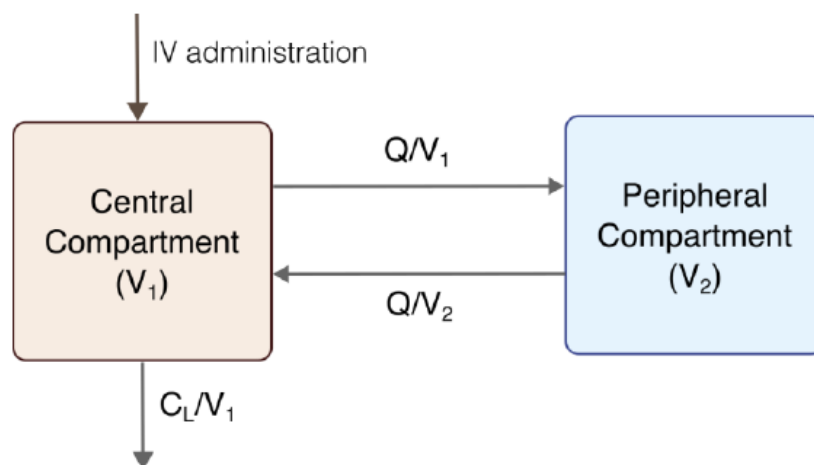
The primary objectives of the PopPK analysis were to assess the PK of cemiplimab in patients with high-risk CSCC after Surgery using an external validation approach with a PopPK model developed for CSCC (without surgery) in adults, and if necessary update the PopPK model with the addition of PK data in adult patients with high-risk CSCC after surgery to generate steady-state exposure predictions in the CSCC population across treatment groups.

The pivotal Phase 3 study 1788 included PK data in patients with high-risk CSCC after surgery and radiation therapy. The patients were randomized to either placebo or IV cemiplimab dosing regimens; 350 mg Q3W 36 weeks (n=59), 350 mg Q3W 12 weeks + 700 mg Q6W 24 weeks (n=112), and 350 mg Q3W >12 weeks + 700 mg Q6W <24 weeks (n=26). Functional cemiplimab concentration was sampled sparsely at predose and end of infusion (EOI) on day (D) 1 of cycle (C) 1, predose of C1D22, C2D1 and C3D1, predose and EOI of C4D1, end of treatment, follow up visit 1 and 2.

The final PK dataset included 197 subjects and a total of 996 samples, of these 67 (6.77%) were post-dose BLQ samples, resulting in 923 quantifiable samples. Pre-dose BLQ samples were set to LLOQ in the analysis dataset and flagged.

External validation was performed using a previously developed model. The reference model was a two-compartment model with linear elimination and a sigmoid elimination function that provided an empirical description of the time-varying change in clearance. Residual variability was modelled using a combined additive and proportional error model. The below figure shows the model structure.

Figure 1: Schematic of 2-Compartment Reference Model With Linear Elimination



CL = clearance; IV = intravenous; Q = intercompartmental clearance; V_1 = volume of distribution of central compartment; V_2 = volume of distribution of peripheral compartment

The covariates retained in the reference model were baseline body weight, sex, time-varying ALB, baseline ALT, CSCC tumor type, and BCC tumor type on clearance; baseline body weight, sex, and baseline albumin on distribution volume; BCC tumor type on E_{max} ; and other tumor type on T_{50} .

An external validation was conducted where the reference model was used to generate post-hoc estimates (only ETA were estimated for each subject) of cemiplimab concentrations for the patients in Study 1788. The initial validation resulted in ETA values with a positive bias, as quantified via one-sample t-tests. To update the reference model, three possibilities were assessed to provide

unbiased ETA values and therefore an unbiased population prediction. The first two possibilities were based on potential CSCC-patient status affecting the time varying clearance: either assuming it doesn't change over time (Model '1' where $CL = CL_0$) or that it has reached the maximal value (Model '2' where $CL = CL_0 \times e^{E_{max}}$). In the third possibility it is assumed that the specific characteristics of the population in Study 1788 (surgery, radiation, high-risk CSCC, etc.) impacted CL and Q (Model '3'). Model 1 had the lowest OFV. The validation of this model resulted in an unbiased ETA related to CL/Q, but with positive bias for the ETA related to Vss. For Model 3 (with the closest OFV to Model 1), the post-hoc random effect distributions of ETA for CL/Q and Vss were approximately normal with no bias. Therefore, Model 3 was selected as the final model, hereafter referred as the 'updated' model. Estimates for covariates on CL and Q (QCL1788) and on Vss (Vss1788) of the updated model were provided in bold in Table 8. All other parameters in Table 2 were fixed from the results in the reference model.

Eta-shrinkage of CL and Q was 32.2% and 26.2% of V1 and V2. Epsilon-shrinkage was approximately 0%.

Table 2: Population Pharmacokinetic Parameter Estimates for the Updated Model

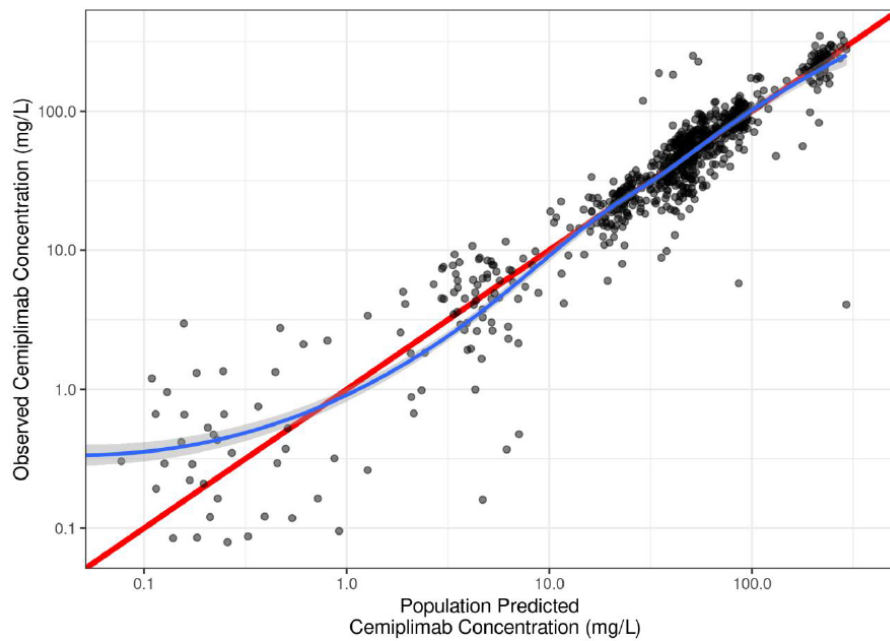
Parameter (Units)	Parameter Estimate (95% CI)	RSE %
Fixed Effects		
CL ₀ : Clearance at baseline (L/day)	0.254 (fixed)	—
V _c : Central Volume of Distribution (L)	3.35 (fixed)	—
Q: Intercompartmental Clearance (L/day)	0.652 (fixed)	—
V _p : Peripheral Volume of Distribution (L)	2.52 (fixed)	—
E _{max} : Typical value of maximum change in CL with time	-0.174 (fixed)	—
T ₅₀ : Typical value of time to reach 50% of the maximum change in CL (day)	73.7 (fixed)	—
Hill: Hill exponent (γ) in the sigmoid E _{max} function describing the change in CL with time	2.50 (fixed)	—
CLWGTBL: Covariate impact of baseline body weight on CL _Q	0.539 (fixed)	—
VSSWGTBL: Covariate impact of baseline body weight on V _c -V _p	0.499 (fixed)	—
CLSEX: Covariate impact of female sex on CL	-0.137 (fixed)	—
VcSEX: Covariate impact of female sex on V _c	-0.0801 (fixed)	—
VCALBBL: Covariate impact of baseline albumin on V _c	-0.217 (fixed)	—
CLALB: Covariate impact of time-varying albumin on CL	-1.11 (fixed)	—
CLALTBL: Covariate impact of baseline alanine aminotransferase on CL	-0.0729 (fixed)	—
CLCSCC: Covariate impact of cutaneous squamous-cell carcinoma (CSCC) tumor type on CL	-0.216 (fixed)	—
QCL1788: Covariate impact specific to the population in Study 1788 on CL and Q	0.1785 (0.0972, 0.2597)	23.25
Vss1788: Covariate impact specific to the population in Study 1788 on V _{ss}	0.1796 (0.1131, 0.2461)	18.88
RE: Residual error	0.241 (fixed)	—
IIV – CL _Q	0.0892 (fixed)	—
IIV – V _c -V _p	0.0709 (fixed)	—

CSCC = cutaneous squamous cell carcinoma; IIV = inter-individual variability; RSE = relative standard error; V₁ = volume of distribution of central compartment; V₂ = volume of distribution of peripheral compartment; V_{ss} = total volume of distribution at steady-state (V_{ss} = V₁ + V₂)

Time dependent clearance was modeled using a sigmoid E_{max} relationship: $CL = CL_0 \times e^{\frac{E_{max} \cdot t^\gamma}{t^\gamma + T_{50}^\gamma}}$.

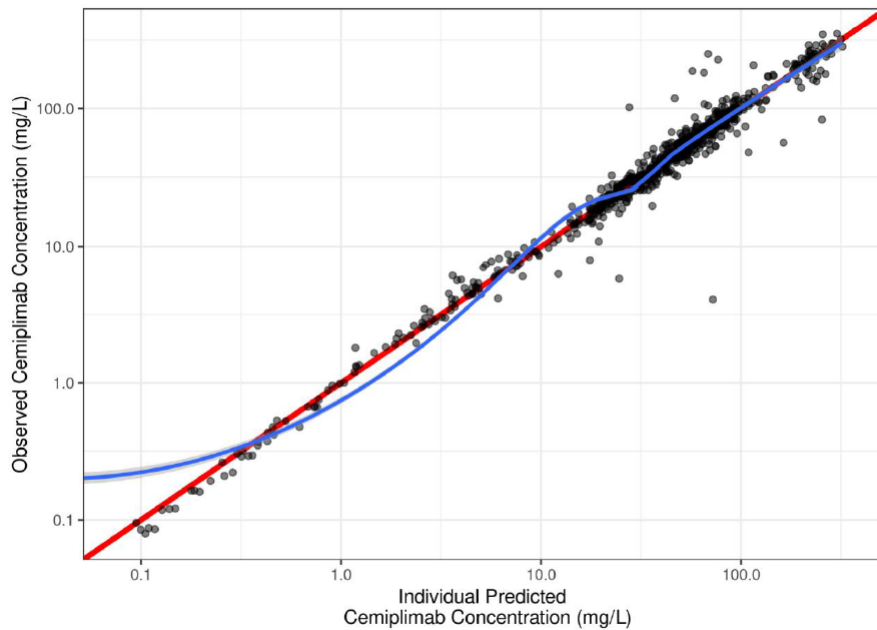
GoF plots were used to evaluate the adequacy of the updated model (Figures 2-3).

Figure 2: Observed vs Population Predicted (PRED) Cemiplimab Concentrations



The solid red line is the line of unity. The blue line is the generalized additive model smoothing line, and the grey shaded region represents the 95% confidence interval of the line.

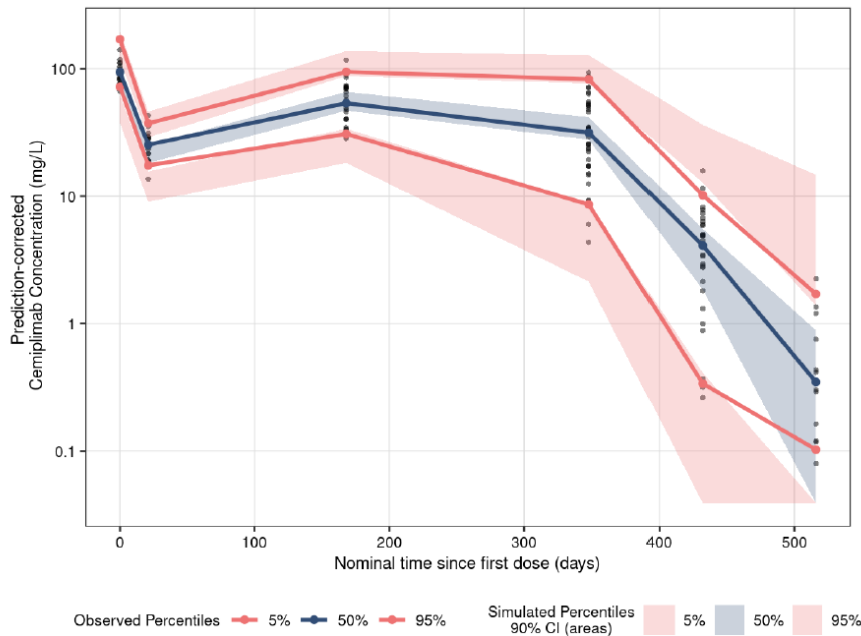
Figure 3: Observed vs Individual Predicted (IPRED) Cemiplimab Concentrations



The solid red line is the line of unity. The blue line is the generalized additive model smoothing line, and the grey shaded region represents the 95% confidence interval of the line.

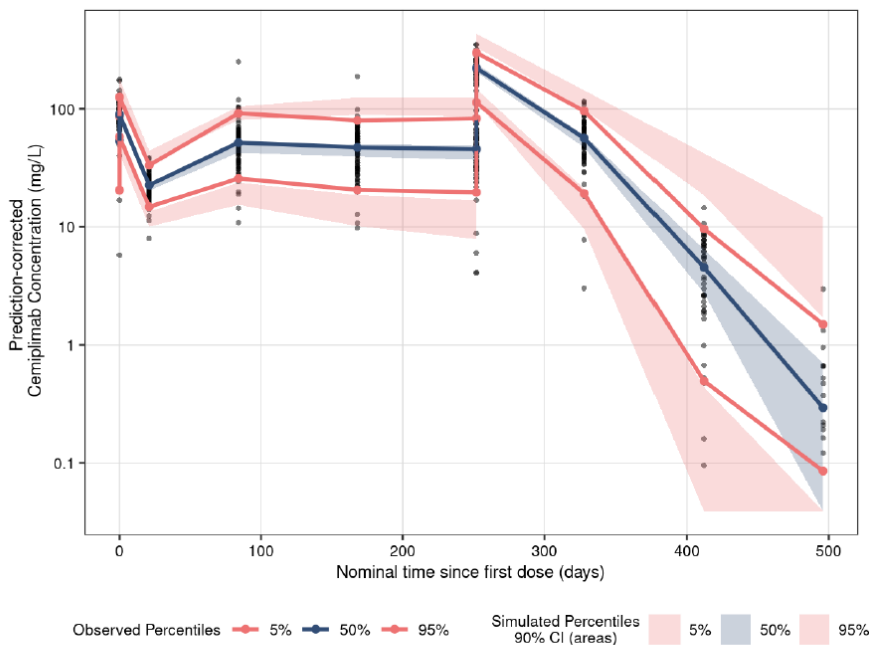
Figure 4 and Figure 5 shows pcVPC plots stratified by treatment regimen.

Figure 4 : External Prediction-Corrected Visual Predictive Check for Treatment Group with 350 mg Q3W Treatment Group Only



BLQ = below the level of quantification; CI = confidence interval; LLOQ = lower limit of quantification;
 Q3W = every three weeks
 The population median is provided by the blue line, and the 5th and 95th percentiles are indicated by the red lines.
 The shaded bands represent the 90% confidence intervals of the median and percentiles generated from the model.
 The observed data is plotted using time since first dose and represented by the black points. Data were grouped by bins at nominal times. The LLOQ of cemiplimab was 0.078 mg/L.

Figure 5: External Prediction-Corrected Visual Predictive Check for Treatment Group with 350 mg Q3W + 700 mg Q6W (Switched at 12 Weeks) Treatment Group

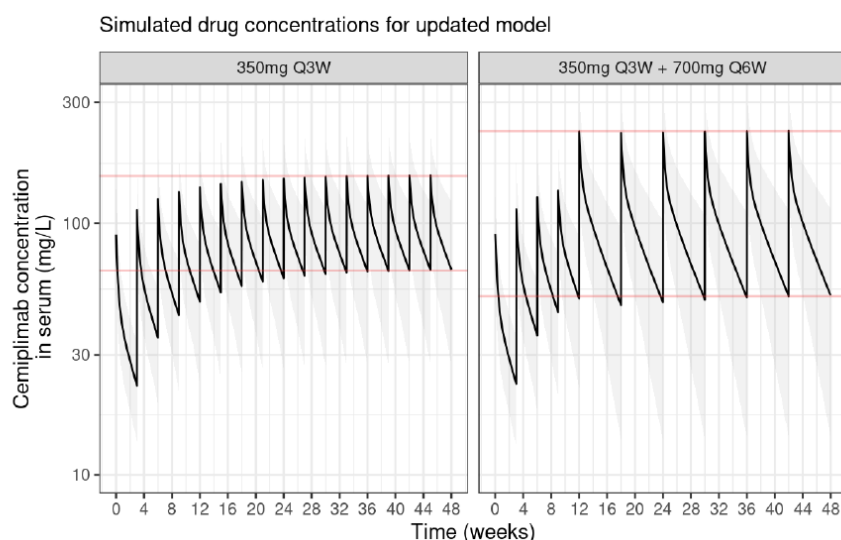


BLQ = below the level of quantification; CI = confidence interval; LLOQ = lower limit of quantification
 The population median is provided by the blue line, and the 5th and 95th percentiles are indicated by the red lines.
 The shaded bands represent the 90% confidence intervals of the median and percentiles generated from the model.
 The observed data is plotted using time since first dose and represented by the black points. Data were grouped by bins at nominal times. The LLOQ of cemiplimab was 0.078 mg/L.

Simulation of extended dosing regimen

The predicted concentration-time profiles with updated model are illustrated in Figure 6. 1000 subjects were sampled with random noise (10% CV) added to covariate values. Predicted population-based steady state exposures using the updated model yielded 20.8% lower $C_{trough,ss}$ values and 51.3% higher $C_{max,ss}$ values for patients who switched to 700 mg Q6W on C2D1, as compared to patients who remained on the 350 mg Q3W regimen.

Figure 6: Exposure Predictions (IPRED) Over Time for Patients with High-Risk CSCC after Surgery



CSCC = cutaneous squamous cell carcinoma; IPRED = individual prediction

The population median is provided by the line, and the 5th and 95th percentiles are indicated by shaded region.

$C_{max,ss}$ and $C_{trough,ss}$ values after infusion at week 36 are indicated by top and bottom solid red lines, respectively.

Reported values are: Mean (SD). N for each treatment group = 1000 subjects; Overall N = 2000 subjects.

Pharmacokinetics in the target population

Study 1788 - Cemiplimab as Adjuvant Therapy in Patients with High-Risk CSCC

Study 1788 is an ongoing, randomized, double-blind, placebo-controlled, multicenter phase 3 study comparing cemiplimab, versus placebo, as adjuvant treatment for patients with CSCC with features associated with high-risk of recurrent disease, who have completed surgery and postoperative radiation therapy, see efficacy section 10.2 and tabular study overview in Section 9.1 for further details.

Cemiplimab dosing regimen in study 1788

Cemiplimab was administered using the approved IV dosing regimen of cemiplimab i.e. 30-min. IV infusion of 350 mg every 3 weeks. With the protocol amendment 2 patients were allowed to switch after 12 weeks of QW3 treatment with 350 mg to 700 mg every 6 weeks (Q6W).

PK -sampling in study 1788

PK samples were collected on cycle 1 day 1 at pre-dose and end-of-infusion and on cycle 1 day 22 at pre-dose; on cycle 2 and 3 day 1 at pre-dose; on cycle 4 day 1 at pre-dose and end-of-infusion; at the EOT visit and the early termination visit.

Pharmacokinetic results in study 1788

The Pharmacokinetic analysis set (PKAS) contains in total 218 patients of which 21 were in the placebo group of the Q3W arm. The PKAS includes 59 patients in the 350 mg Q3W cemiplimab cohort only and 138 patients in the 350 mg Q3W start/750 mg Q6W cemiplimab cohort (switch regimen cohort). Out of these 138 patients the majority of patients (n=112) switched at Week 12 and the rest after week 12.

Cemiplimab serum concentrations at each timepoint were summarized by descriptive statistics, see table 3 and figure 7.

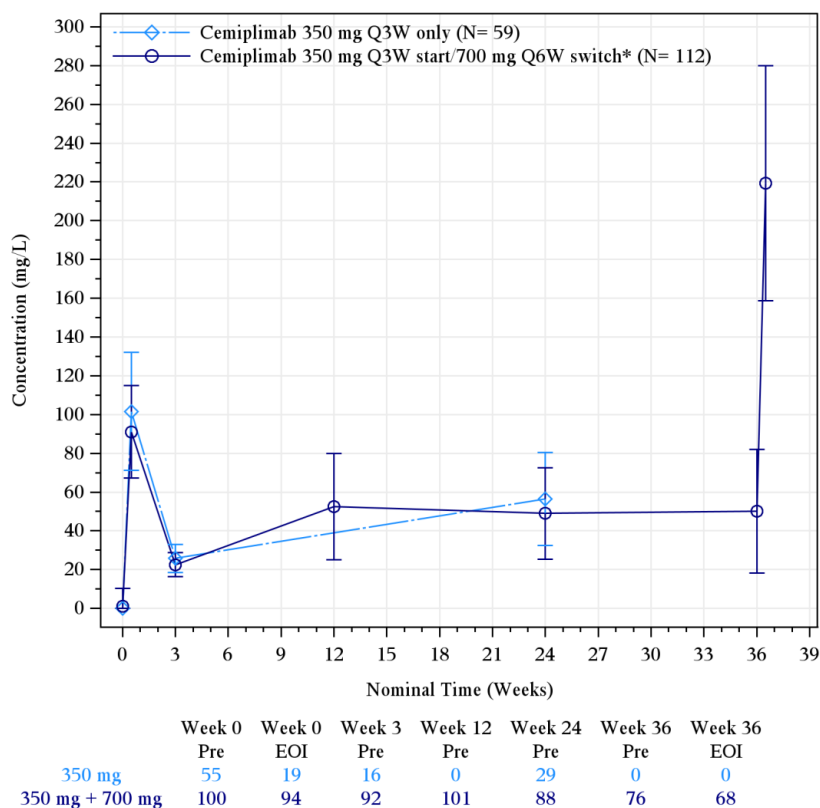
Table 3: Summary of Observed Concentrations of Functional Cemiplimab in Serum by Time and Treatment Arm in Participants with High-Risk CSCC (Study R2810-ONC-1788, PKAS)

Visit Timepoint	Concentrations of Functional Cemiplimab in Serum (mg/L)			
	Cemiplimab 350 mg Q3W only (N=59)		Cemiplimab 350 mg Q3W start/ 700 mg Q6W switch* (N=112)	
	n	Mean (SD)	n	Mean (SD)
Cycle 1 Day 1 (Week 0)				
Pre-Dose	55	0 (0)	100	1.07 (9.19)
End of Infusion	19	102 (30.4)	94	91.1 (23.7)
Cycle 1 Day 22 (Week 3)				
Pre-Dose	16	25.8 (7.24)	92	22.6 (6.29)
Cycle 2 Day 1 (Week 12)				
Pre-Dose	0		101	52.5 (27.4)
Cycle 3 Day 1 (Week 24)				
Pre-Dose	29	56.5 (23.9)	88	49.0 (23.7)
Cycle 4 Day 1 (Week 36)				
Pre-Dose	1	66.7 (---)	76	50.1 (32.0)
End of Infusion	0		68	219 (60.7)

Note: Below LLOQ value is set to 0.

* Includes only those switched to 700 mg Q6W at Week 12 (Cycle 2 Day 1) as per Protocol Amendment 2.

Figure 7: Mean (SD) Observed Concentrations of Functional Cemiplimab in Serum by Nominal Time and Treatment Arm in Participants with High-Risk CSCC (Study R2810-ONC-1788, PKAS)



Note: Below LLOQ values is set to 0. Table under the figure presents the number contributing to the statistics for the corresponding visits and treatment arms.

* Includes only those switched to 700 mg Q6W at Week 12 (Cycle 2 Day 1) as per Protocol Amendment 2.

Comparison of Q3W and Q6W dosing regimen by population PK analysis prior to study start

PK modeling and simulation were conducted to evaluate the impact in PK by a switch from a dosing regimen of 350 mg Q3W to 700 mg Q6W at week 12. The model-predicted steady state cemiplimab exposures ($C_{trough, ss}$, $C_{max, ss}$, and $C_{avg, ss}$) of the two dosing regimens are provided in Table 4 (previous reference Pop-PK model), table 5 (updated Pop-PK model) and in figure 8.

Table 4: Predictions of Cemiplimab's exposure at Steady State for 700 mg IV Q6W regimen compared to 350 mg IV Q3W regimen in 1063 Patients (reference Pop-PK model)

Exposure Metric	Dosing Regimen	Mean (CV%)	Percent Difference from Reference
$C_{trough, ss}$ (mg/L)	350 mg Q3W*16 IV	60.4 (47.4%)	--
	350 mg Q3W*4 IV+700 mg Q6W*6 IV	42.1 (59.2%)	-30.3%
$C_{max, ss}$ (mg/L)	350 mg Q3W*16 IV	172 (27.6%)	--
	350 mg Q3W*4 IV+700 mg Q6W*6 IV	265 (25.9%)	54.3%
$C_{avg, ss}$ (mg/L)	350 mg Q3W*16 IV	90.4 (37.2%)	--
	350 mg Q3W*4 IV+700 mg Q6W*6 IV	90.4 (37.3%)	0%

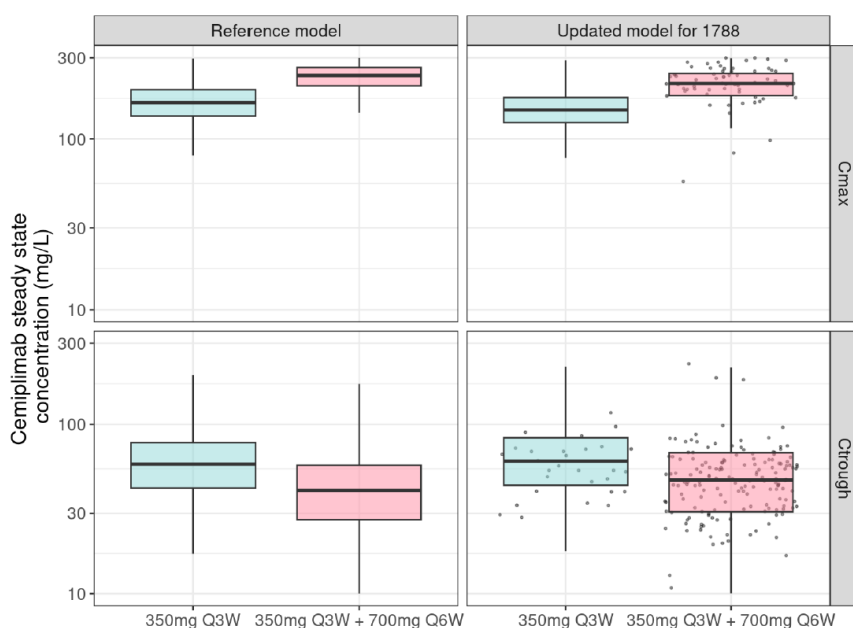
Table 5: Exposure Predictions by Treatment Group for Cemiplimab in Patients with High Risk CSCC after Surgery (updated Pop-PK model) -Data from Study 1788

Treatment	Steady State (36 Weeks)	
	C_{max} [mg/L]	C_{trough} [mg/L]
350 mg Q3W	154 (43.1)	66.3 (30.7)
350 mg Q3W + 700 mg Q6W	233 (64.9)	52.5 (31.4)

C_{max} = maximum concentration; CSCC = cutaneous squamous cell carcinoma; C_{trough} = trough concentration; SD = standard deviation

Reported values are: Mean (SD). N for each treatment group = 1000 subjects; Overall N = 2000 subjects.

Figure 8: $C_{max,ss}$ and $C_{trough,ss}$ Estimates for the Reference and Updated Models. Compared to Observed Data From Study 1788



2.3.3. Pharmacodynamics

No new PD studies have been performed for the actual submission.

Exposure-response analyses for efficacy and safety based on data from the first-in-human Study 1423 and on data from Study 1540 were previously described in the initial submission for advanced CSCC. Overall, no meaningful exposure-response relationships for either efficacy or safety were observed; there was no evidence supporting the need for a dose adjustment over the range of exposures studied. These analyses resulted in a flat relationship between cemiplimab exposure and safety endpoints at the doses studied.

Due to the lack of relationships for exposure-safety and exposure-efficacy in advanced CSCC and other indications at relevant doses, exposure-response analyses were not performed for the current submission supporting the use of cemiplimab in the adjuvant setting for patients with high-risk CSCC.

Immunogenicity

Table 6: Summary of ADA status, ADA category, and maximum titer category (AAS)

Table 58: Summary of ADA Status, ADA Category, and Maximum Titer Category by Treatment Arm in Participants with High-risk CSCC (AAS)

Analysis Set	Cemiplimab		Placebo	
	350 mg Q3W only N (%)	350 mg Q3W start/700 mg Q6W switch N (%)	Q3W only N (%)	Q3W start/Q6W switch N (%)
ADA				
ADA Analysis Set	17 (100%)	131 (100%)	6 (100%)	133 (100%)
Negative	17 (100%)	124 (94.7%)	6 (100%)	123 (92.5%)
Pre-existing Immunogenicity	0	5 (3.8%)	0	7 (5.3%)
TB Response	0	0	0	0
TE Response	0	2 (1.5%)	0	3 (2.3%)
Persistent	0	0	0	3 (2.3%)
Transient	0	1 (0.8%)	0	0
Indeterminate	0	1 (0.8%)	0	0
TE & TB Maximum Titer Category				
Low (<1000)	0	2 (1.5%)	0	3 (2.3%)
Moderate (1000 to 10000)	0	0	0	0
High (>10000)	0	0	0	0

Abbreviations: AAS, ADA analysis set; ADA, Anti-drug antibody; CSCC, Cutaneous squamous cell carcinoma; Q3W, Every 3 weeks; Q6W, Every 6 weeks; TB, Treatment-boosted; TE, Treatment-emergent

Note: Percentages are based on AAS for ADA status, subcategories, and titer categories.

Source: Table 5 in Appendix 16.1.14

Due to the low immunogenicity across previous studies, with no corresponding impact on cemiplimab concentrations based on analysis of human samples, assessment of neutralizing activity in ADA positive samples was not performed in this study.

Due to the lack of relationships for exposure-safety and exposure-efficacy in advanced CSCC and other indications at relevant doses, exposure-response analyses were not performed for the current submission.

2.3.4. Discussion on clinical pharmacology

The application is primarily based on results of the clinical study R2810-ONC-1788 (referred to as 1788), investigating cemiplimab as adjuvant therapy versus placebo, in patients with CSCC with features associated with high-risk of recurrent disease who have completed surgery and post-operative radiation therapy. Two IV dosing regimens were investigated in addition to placebo: 350 mg IV Q3W (approved in other cancer indications) and a novel extended dosing regimen, i.e. 350 mg IV Q3W for 12 weeks, followed by 700 mg IV Q6W. A minor part of the patients was switched to the extended dosing regimen later than 12 weeks.

Cemiplimab in serum samples from study 1788 was quantified with previously validated Elisa method and the bioanalysis was conducted according to regulatory requirements. Immunogenicity of cemiplimab in study 1788 was adequately investigated with previously validated ADA method.

Appropriate software and methods were used for PK data analysis. The reference PopPK model used for external validation was a 2-compartment model with linear elimination and a sigmoid elimination function to describe time-varying of clearance. Residual variability was modelled using a combined additive and proportional error model. Including data from study 1788 resulted in biased ETA values. To remove bias the reference model was updated to include the additional covariates QCL1788 and Vss1788, all previous model parameters were fixed. Epsilon-shrinkage of the updated model was <20%, eta-shrinkage was >20%. The high eta-shrinkage may hide or induce EBE-EBE correlations or covariate relationships. GOF plots showed underprediction of low cemiplimab concentrations. The updated PopPK model was used to simulate cemiplimab concentration predictions of 1000 subjects for each of the dosing regimens. No exposure-response analyses were performed for the current submission.

The pharmacokinetics of cemiplimab was investigated in the study 1788 using sparse PK-sampling i.e. mainly C_{predose} (C_{trough}) and C_{eo} (C_{max}) samples. The mean C_{trough}, Cycle 3, day 1 (56.4 mg/L) with the standard regimen of 350 mg Q3W was slightly lower, though in range, with mean C_{trough} data (63.9 mg/L) in advanced CSCC (metastatic and locally advanced CSCC), study 1540, see [EPAR EMEA/H/C/004844/0000](https://www.ema.europa.eu/en/medicines/human/EPAR/KEYTRUDA/keytruda-epar-public-assessment-report). Cemiplimab's PK is thus considered to be similar in the different CSCC populations. With the extended dosing regimen, the mean C_{trough}, Cycle 3, day 1 (49.0 mg/L) was further reduced, as expected when the dose and dosing interval is doubled. The two dosing regimens PK were also evaluated using the reference and updated Pop-PK model. For a virtual population of 1000 subjects, using the updated Pop-PK model, it was estimated that mean C_{max} was approx. 51% higher and that mean C_{trough} 21% lower for the extended dosing regimen vs standard dosing regimen of cemiplimab. The SmPC section 5.2 reflects the updated population PK model with the additional 1000 virtual patients per regimen (table 4). In these patients, at 350 mg Q3W for 12 weeks followed by 700 mg Q6W for 36 additional weeks, the mean cemiplimab concentrations at steady-state ranged between a C_{trough} of 52.5 mg/L and a concentration at end of infusion (C_{max}) of 233 mg/L, while at 350 mg Q3W for 36 weeks, the mean cemiplimab concentrations at steady-state ranged between a C_{trough} of 66.3 mg/L and a concentration at end of infusion (C_{max}) of 154 mg/L.

Comparable results were obtained with the reference Pop-PK model. AUC_{ss} was unchanged as expected for a drug product having linear PK.

As the PK of cemiplimab, in particular C_{trough}, using the extended dosing regimen is considered to be in the range of linear PK and as a flat concentration-response relationship is expected from previous data in similar cancer populations, it is expected that the efficacy/safety profile will be comparable using the extended dosing regimen as the standard dosing regimen.

No new PD data or exposure-analyses have been provided in this submission. This is acceptable since Libtayo is well characterised in other indications and no relationship between exposure-response and/or exposure safety was observed previously. In the 1788 study, there was a low incidence of immunogenicity (1.5% in 350mg Q3W and 2.3% in SWITCH regime). These results are in line with the low immunogenicity of cemiplimab observed in previous clinical studies.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology of cemiplimab in high risk CSCC patients was adequately investigated in the clinical study 1788, in which a new extended 700 mg Q6W dosing scheme of cemiplimab was investigated. The duration of adjuvant treatment of up to 48 weeks is also agreed. Furthermore, the established Pop-PK model of cemiplimab was updated for the population of high risk CSCC patients. In conclusion, the clinical pharmacology is supportive for approval.

Table 7: Definition of high-risk criteria

Nodal and Non-nodal High-risk Criteria				
Nodal disease Inclusion 3a	In-transit metastases Inclusion 3b	Perineural invasion Inclusion 3c	T4 lesions Inclusion 3d	Recurrent CSCC Inclusion 3e
ECE with ≥ 1 node ≥ 20 mm OR ≥ 3 nodes regardless of ECE	Skin or subcutaneous metastases > 2 cm from the primary lesion but not beyond the regional nodal basin	Clinical and/or radiologic involvement of named nerves	Invasion of cortical bone or skull base	CSCC that arises within the area of previously resected tumor, plus ≥ 1 additional feature*
*Additional features for 3e recurrent lesion $\geq N2b$ (multiple ipsilateral nodes) $\geq T3$ (≥ 4 cm diameter or bone erosion or invasion > 6 mm) - Poorly differentiated histology and recurrent lesion ≥ 20 mm diameter.				

Note: Tumors with nodal and non-nodal criteria were categorized as nodal.

Abbreviations: CSCC, Cutaneous squamous cell carcinoma; ECE, extracapsular extension, HN, Head and neck; LN, Lymph nodes; T, Tumor stage

Study participants

Main inclusion criteria per the latest protocol version:

- Men and women ≥ 18 years old (for Japan only, men and women ≥ 21 years old)
- Patient with resection of pathologically confirmed CSCC (primary CSCC lesion only, or primary CSCC with nodal involvement, or CSCC nodal metastasis with known primary CSCC lesion previously treated within the draining lymph node echelon), with macroscopic gross resection of all disease.
- High risk CSCC, as defined by at least 1 of the following:
 - Nodal disease with (i) extracapsular extension (ECE)* and at least 1 node > 20 mm on the surgical pathology report, and/or (ii) ≥ 3 lymph nodes positive on surgical pathology report, regardless of ECE.

*ECE is defined as extension through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. Unambiguous evidence of gross ECE (defined as invasion of skin, infiltration of musculature/fixation to adjacent structures on clinical examination) is a sufficiently high threshold to classify these as ECE positive (AJCC, 2017).

- In-transit metastases (ITM), defined as skin or subcutaneous metastases that are > 2 cm from the primary lesion but are not beyond the regional nodal basin (Leitenberger, 2016).
- T4 lesion, including HN lesions (AJCC, 2017) and non-HN lesions (UICC, 2015).
- Perineural invasion (PNI), defined as clinical and/or radiologic involvement of named nerves (UICC, 2015).
- Recurrent CSCC, defined as CSCC that arises within the area of the previously resected tumor, plus at least 1 of the following additional features (AJCC, 2017):

- $\geq$ N2b disease associated with the recurrent lesion
 - Nominal $\geq$ T3 (recurrent lesion $\geq$ 4 cm in diameter or minor bone erosion or deep invasion $>$ 6 mm measured from the granular layer of normal adjacent epithelium).
 - Poorly differentiated histology and $\geq$ 20 mm diameter of recurrent lesion.
 - The recurrent tumor must be documented to be within the area of the previously resected CSCC by radial measurement of the greatest radius of the final defect, measured from the estimated center of the original surgical wound.
4. Completion of curative intent post-operative RT (concurrent chemoradiotherapy is acceptable) within 2 to 10 weeks of randomization. Patients must have received a minimum Biologically Equivalent Dose (BED) to the site of previous gross disease of 50 Gy (for head and neck primary sites and non-head and neck primary sites).
 5. Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$ 1.
 6. Adequate hepatic, renal and bone marrow function
 7. Must be willing and able to provide informed consent signed by study patient or legally acceptable representative, as specified by health authorities and institutional guidelines.
 8. Toxicities from radiotherapy must have resolved to grade 1 or less except the following toxicities, which must have resolved to grade 2 or less: dysgeusia, fatigue, xerostomia, trismus, alopecia, fibrosis, oropharyngeal mucositis, dermatitis, skin ulceration, or edema in radiated field.
 9. Willing and able to comply with clinic visits and study-related procedures
 10. Able to understand and complete study-related questionnaires

Main exclusion criteria:

1. Squamous cell carcinomas (SCCs) arising in non-cutaneous sites (eg, dry red lip [vermillion], oral cavity, oropharynx, paranasal sinus, larynx, hypopharynx, nasopharynx, salivary gland, nasal mucosa, anogenital area, or SCC nodal metastasis with unknown primary).
2. Concurrent malignancy other than localized CSCC and/or history of malignancy other than localized CSCC within 3 years of date of randomization, except for tumors with negligible risk of metastasis or death, such as adequately treated (BCC) of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or low-risk early stage prostate adenocarcinoma (T1-T2aN0M0 and Gleason score $\leq$ 6 and prostate-specific antigen (PSA) $\leq$ 10 ng/mL) for which the management plan is active surveillance, or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of $>$ 12 months for which the management plan is active surveillance (D'Amico, 2005) (Pham, 2016).
3. Patients with hematologic malignancies (note: patients with chronic lymphocytic leukemia [CLL] are not excluded if they have not required systemic therapy for CLL within 6 months of enrollment).
4. Patients with history of distantly metastatic CSCC (visceral or distant nodal), unless the disease-free interval is at least 3 years (regional nodal involvement of disease in draining lymph node basin that was resected and radiated prior to enrollment will not be exclusionary, per exclusion criterion 2).

5. Ongoing or recent (within 5 years of randomization date) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
6. Has participated in a study of an investigational agent or an investigational device within 4 weeks of the randomization date or five half-lives (whichever is longer), though patients who have received or are enrolled in a study involving treatment with an investigational immunoPET reagent are not excluded.
7. Receipt of a live vaccine within 28 days of the randomization date
8. Has had prior systemic anti-cancer immunotherapy for CSCC. Examples of immune modulating agents include but are not limited to blockers of CTLA-4, 4-1BB (CD137), or OX-40, therapeutic vaccines, anti-PD-1/PD-L1 or PI3K δ inhibitors.
9. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab/placebo.
10. Has received treatment with an approved anticancer systemic therapy within 4 weeks of the randomization date or has not yet recovered from any acute toxicities except for laboratory changes as described in inclusion criteria 6, 7, and 8.
11. Prior allogeneic stem cell transplantation, or autologous stem cell transplantation.
12. Patients who have permanently discontinued anti-cancer immune modulating therapies due to drug-related toxicity.
13. Encephalitis, meningitis, or uncontrolled seizures in the year prior to screening/enrollment.
14. Patients with myocardial infarction within 6 months prior to the randomization date.
15. Any infection requiring hospitalization and/or intravenous antibiotic therapy within 2 weeks of the randomization date.
16. Active tuberculosis.
17. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C virus (HBV or HCV) infection; or diagnosis of immunodeficiency.
18. History of immune related pneumonitis within the last 5 years
19. History of interstitial lung disease (e.g., idiopathic pulmonary fibrosis, organizing pneumonia) or active, noninfectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management. A history of radiation pneumonitis in the radiation field is permitted as long as pneumonitis resolved $\geq$ 6 months prior to the randomization date.
20. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments.
21. Known hypersensitivity or allergy to any of the excipients in the cemiplimab drug product.
22. Patients with a history of solid organ transplant (patients with prior corneal transplant(s) are not excluded).

23. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study.
24. Known psychiatric or substance abuse disorders that would interfere with participation with the requirements of the study.

Treatments

In the original protocol eligible patients were randomized to:

- Cemiplimab 350 mg every 3 weeks (Q3W) intravenous (IV) for up to 48 weeks vs
- Placebo Q3W for up to 48 weeks

After implementation of **protocol amendment 2** patients received:

- Cemiplimab 350 mg Q3W IV for up to 12 weeks followed by cemiplimab 700 mg every 6 weeks (Q6W) IV for up to 36 additional weeks for up to 48 weeks total vs
- Placebo IV Q3W for up to 12 weeks followed by placebo IV Q6W for up to 36 additional weeks for up to 48 weeks total.

Table 8: Administered study interventions

Intervention Name	Cemiplimab/Cemiplimab-rwlc/Libtayo®/REGN2810	Placebo
Type	Biologic	Not applicable
Dose Formulation	Liquid	Liquid
Unit Dose Strengths	350 mg	Dose strength is not applicable. Placebo will be prepared using the same formulation as that used for cemiplimab without the addition of active substance.
Dosage Frequency	350 mg Q3W for 48 weeks; 350 mg Q3W for 12 weeks followed by 700 mg Q6W after 12 weeks for an additional 36 weeks for a total treatment duration of 48 weeks	Same frequency as cemiplimab
Route of Administration	30-min IV infusion	30-min IV infusion
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Packaging, storage, and labeling details are provided in the pharmacy manual.	Packaging, storage, and labeling details are provided in the pharmacy manual.

Abbreviations: IMP, Investigational medicinal product; IV, Intravenous; NIMP, Non-investigational medicinal product; Q3W, Every 3 weeks; Q6W, Every 6 weeks

Duration of treatment: All patients were treated until disease recurrence, unacceptable toxicity, for up to 48 weeks of total therapy.

Crossover: Patients who experienced disease recurrence in both treatment arms (for patients in the experimental arm who experience **disease recurrence ≥3 months** after completing 48 weeks of planned cemiplimab treatment) had an option to participate in part 2 study (open-label) and receive cemiplimab for up to 96 weeks.

Dose modifications were not allowed. Dose delays were permitted.

Prohibited medications and procedures:

- Standard or investigational agent for treatment of a tumor other than cemiplimab or placebo, with the exception of those listed in the protocol.
- Agents that block the PD-1/PD-L1 pathway (other than for patients who are assigned to receive cemiplimab in the study).
- Radiation therapy
- Live vaccines for at least 3 months after the last dose of study drug.

Permitted medications and procedures:

- Any medication required to treat an AE and/or irAE, including systemic corticosteroids
- Systemic corticosteroids for physiologic replacement (even if >10 mg/day prednisone equivalents)
- A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions
- Oral contraceptives, hormone-replacement therapy, or other maintenance therapy may continue
- Surgical resection of pre-malignant lesions or BCC lesions
- Other medications and procedures may be permitted on an individual basis by the investigator and in consultation with the sponsor
- surgery for any emergent medical issue(s) is clinically indicated in the opinion of the investigator for an individual patient

Study assessments:

Imaging assessments were performed at screening and at the end of each 12-week cycle during the planned treatment period of approximately 1 year (48 weeks). Imaging assessments were less frequent in the follow-up period: patients undergo imaging assessments every 4 months during the first 2 years of planned follow-up and every 6 months thereafter. During each imaging assessment, radiologic imaging of the chest, abdomen, and pelvis is required in form of CT scans and/or MRI. For patients in which the resected lesion was in the HN, imaging of the neck will be obtained.

Biopsy to obtain histologic or cytologic evidence of CSCC should be attempted in all cases of suspected recurrence or suspected second primary cutaneous squamous cell carcinoma tumor (SPT) unless biopsy is considered to pose an unacceptable safety risk in the opinion of the investigator (e.g., brain lesions).

Biomarker analyses:

The study included a pre-specified exploratory analysis for comparison of DFS between patients treated with adjuvant cemiplimab and those treated with placebo within the PD-L1 biomarker subsets defined by $\geq 1\%$ and $< 1\%$ viable tumor cell expression (also referred to as tumor proportion score; TPS). The PD-L1 TPS was assessed IHC with the use of the Ventana SP263 assay (Roche Diagnostics).

Patient-Reported Outcomes in Part 1 of the Study (PRO): PRO data were evaluated based on the EORTC QLQ-C30 and EQ-5D-3L questionnaires. EORTC QLQ-C30 and EQ-5D-3L were administered at day 1 of every cycle, end of treatment, and during follow-up in Part 1. Pre-specified analyses included (1) descriptive analyses, (2) overall changes from baseline across treatment cycles using mixed effects models for repeated measures, (3) PRO responder analysis (which categorizes patients into meaningful improvement, maintenance, or worsening of their PRO scores from baseline) at each cycle using a

published threshold of 10 points for a meaningful change in the EORTC QLQ-C30 GHS/QoL scale or 7 points for the EQ-5D-3L VAS, and (4) median time to first deterioration, using the same meaningful within-person change thresholds for deterioration (10 points for the EORTC QLQ-C30 GHS/QoL scale, 7 points for the EQ-5D-3L VAS) using Kaplan-Meier analyses.

Definitions of disease recurrence:

1. Locoregional:

- For HN CSCC, nodal or soft tissue recurrence above the clavicle.
- For non-HN CSCC, recurrence within the first draining nodal basin (or soft tissue associated within the first draining nodal basin) of the resected tumor.
- In-transit metastases, defined as skin or subcutaneous metastases that are > 2 cm from the primary lesion but are not beyond the regional nodal basin

2. Distant:

- For HN CSCC, nodal recurrence below the clavicle.
- For non-HN CSCC, recurrence beyond the first draining nodal basin of the resected tumor bed. Recurrence in 2 nodal basins will be considered distant recurrence, even if contiguous (i.e., 2 mediastinal nodal basins, 2 pelvic nodal basins).
- Recurrence in non-nodal tissue (including, but not limited to, lung, liver, bone, brain).
- Epidermotropic metastases, defined as distant lesion(s) in the dermis without epidermal involvement.

In this study, **a new CSCC lesion** arising on the skin during the study period will be classified as an SPT unless the lesion represents ITM or EDM. Second primary CSCC tumors are not counted as events for the DFS endpoint. Patients who develop ITM or EDM will be considered to have experienced a DFS event. Second primary CSCC tumors arising during the study period should be treated with surgery or another permitted local modality. Permitted non-surgical local modalities for SPTs in this study are: topical 5-fluorouracil, topical imiquimod, and photodynamic therapy with topical aminolevulinic acid or methyl aminolevulinate (Christensen, 2018).

Objectives/endpoints

The primary objective of the study is to compare DFS (disease free survival) of patients with high-risk CSCC treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT.

Table 9: Objectives with respective endpoints for Study 1788

Objectives	Endpoints
Primary	
The primary objective of the study is to compare DFS of patients with high-risk CSCC treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT.	The primary endpoint of the study is DFS, defined as time from randomization to the first documented disease recurrence (local, regional, and/or distant) or death due to any cause. For patients who did not have a tumor recurrence or death, DFS will be censored on the date of last disease assessment.
Secondary	
To compare the OS of high-risk CSCC patients treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT.	OS, defined as time from randomization to the date of death. A patient who has not died will be censored on the last known date as alive.
To compare the effect of adjuvant cemiplimab with that of placebo on patients' FFLRR after surgery and RT.	FFLRR, defined as time from randomization to the date of first LRR. Patients who died without a preceding LRR will be censored on the date of death. For patients who did not have a LRR or death, FFLRR will be censored on the date of last disease assessment.
To compare the effect of adjuvant cemiplimab with that of placebo on patients' FFDR after surgery and RT.	FFDR, defined as time from randomization to the date of first DR. Patients who died without a preceding DR will be censored on the date of death. For patients who did not have a DR or death, FFDR will be censored on the date of last disease assessment.
To compare the effect of adjuvant cemiplimab with that of placebo on the cumulative incidence of SPTs after surgery and RT.	Cumulative occurrence of SPTs for each patient from randomization to occurrence of first primary endpoint event or EOS.
To evaluate the safety of adjuvant cemiplimab and that of placebo in high-risk CSCC patients after surgery and RT.	Safety, as measured by the incidence and severity of TEAEs, deaths, and laboratory abnormalities.
To assess cemiplimab PK and immunogenicity in human serum.	Cemiplimab concentrations in serum and immunogenicity as measured in ADA in serum.
Tertiary/Exploratory	
To evaluate the pattern of failure of high-risk CSCC patients treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT.	Pattern of failure, assessed using descriptive analysis of percentages of patients in which disease recurrence for the primary endpoint of the study is due to local recurrence, regional recurrence, or DR.
To explore the geographic/regional variations in administration of post-operative RT for the high-risk CSCC patients enrolled in the study.	Geographic variations in administration of post-operative RT.
To compare the HRQoL of high-risk CSCC patients treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT.	- HRQoL, as assessed by the EORTC QLQ-C30. - General health status and health utility, as assessed using the EQ-5D-3L.
To explore associations between the clinical efficacy of cemiplimab and molecular features in pretreatment tumor samples.	Association between the clinical efficacy of cemiplimab and molecular features of pretreatment tumor samples.

Sample size

Enrollment of 412 patients is assumed to occur over approximately 48 months. A dropout rate of 5% per year is assumed. The sponsor assumes DFS probability of 55% at 3 years in the placebo group. The statistical design of this study assumes a HR of 0.6 between the cemiplimab group and the placebo group. The patients will be randomized in a 1:1 ratio.

With 3 planned interim analyses using Lan-DeMets O'Brien-Fleming spending function, under these assumptions 165 DFS events will yield 90% power to detect the difference between treatment arms with type I error of 0.05 (2-sided).

Randomisation

Patients were randomized in a 1:1 ratio in a blinded fashion to receive either cemiplimab or placebo according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

Randomization was stratified by:

- Anatomic region of resected high-risk tumor: HN vs non-HN (Head and neck).
- Geographic Region: North America vs Australia/New Zealand vs Rest of World (ROW)
- High risk feature (nodal versus exclusively non-nodal). For example, if the patient meets high-risk criteria with both nodal and non-nodal features, they will be considered in the nodal stratum.
- ECOG PS: 0 vs 1 (Eastern Cooperative Oncology Group Performance Status)
- History of CLL (Chronic lymphocytic leukemia): presence or absence

The stratification factors "high risk features", "ECOG PS" and "history of CLL" are used for balancing treatment assignment only and not included in the statistical model for analysis of the primary endpoint.

Blinding (masking)

Part 1 addresses the primary DFS endpoint of the study and is placebo-controlled and double-blinded.

All imaging and on-study biopsy results from a randomly selected sample of patients will be reviewed in a blinded fashion by an Independent Review Committee (IRC) to assess concordance with the investigator-assessed results.

Statistical methods

Analysis sets:

The full analysis set (FAS) includes all randomized patients. This is the intent-to-treat population. The FAS is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug.

The ADA analysis set includes all patients who received any study drug and had at least 1 non-missing ADA result following the first study dose.

Primary hypothesis:

The primary clinical hypothesis of the study is that cemiplimab prolongs the DFS as compared with placebo. The primary analysis of DFS will be performed with a 2-sided alpha at a 0.05 overall significance level for the following null and alternative statistical hypotheses:

H0: The survival curve of DFS for cemiplimab is the same as that for placebo

H1: The survival curve of DFS for cemiplimab is not the same as that for placebo

Primary endpoint, definition and censoring:

The primary endpoint of the study is DFS, defined as time from randomization to the first documented disease recurrence (local, regional and/or distant) by investigator assessment or death due to any cause, whichever occurs first. The date of disease recurrence is determined according to the following rules:

- Radiologic Evidence with Confirmatory Pathology Sample: If the pathology sample is obtained prior to the imaging, the date of the procedure to obtain the pathology sample will be the date of recurrence. If the pathology sample is obtained after the imaging, and if the biopsy procedure date is within 21 days of the imaging date, the recurrence date will be the date of the imaging assessment. If the procedure date that confirms pathologic recurrence is performed more than 21 days after the most recent imaging, the biopsy procedure date will be the date of recurrence.
- Pathologic Evidence Only: the biopsy procedure date will be the date of disease recurrence.
- Radiologic Evidence Only: the imaging date will be the date of disease recurrence.

For patients who do not have a tumor recurrence or death, DFS will be censored on the date of last disease assessment. For patients who remain alive and have no post-baseline disease assessments after randomization, DFS will be censored on the day of randomization.

Primary Efficacy Analysis

The primary endpoint of DFS will be tested using the stratified log-rank test at 2-sided 0.05 significance level using anatomical region of resected high-risk tumor (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) as stratification factors.

Analyses will be based on FAS according to the treatment group and strata assigned at randomization. Kaplan-Meier estimates including DFS median and DFS rate at the end of each year, along with 2-sided 95% CIs, will be presented for each treatment group. Kaplan-Meier curves will be presented for each treatment group.

The HR of DFS and its 95% CI will be estimated by a stratified Cox Regression model using the treatment group as a covariate and the same stratification factors as for the log-rank test. Subgroup analyses may be performed to determine the consistency of treatment effect across various demographics and baseline characteristics. Between-group treatment effect, along with its nominal 95% CI, for the primary endpoint will be estimated for each of the following subgroups:

- Age (<65 years, ≥65 years)
- Gender (Male, Female)
- Race (White, Non-white)
- Anatomic region of resected high-risk tumor (HN, Non-HN)
- Geographical region (North American, Australia/New Zealand, ROW)
- High risk feature (Nodal, exclusively Non-Nodal)
- ECOG status (0, 1)
- History of CLL (presence or absence)

Primary and sensitivity estimand for DFS:

Table 10: Estimand Framework for Study 1788

Estimand Attribute	Description		
Population	Participants with CSCC at high-risk of recurrent disease, after surgery and radiation therapy (RT).		
Treatment	Experimental arm: cemiplimab Control arm: placebo		
Endpoint	DFS, defined as time from randomization to the first documented disease recurrence (local, regional and/or distant) by investigator assessment or death due to any cause, whichever occurs first.		
Intercurrent Events (ICEs)	Event	Strategy	Description
	Discontinuation of treatment prior to disease recurrence or death	Treatment policy strategy	All data collected, regardless of any occurrence of this ICE, will be used in the analysis.
	Start of new anti-cancer therapy	Treatment policy strategy <i>Sensitivity analysis: Hypothetical strategy</i>	All data collected, regardless of any occurrence of this ICE, will be used in the analysis. <i>Sensitivity analysis: Participants will be censored at last evaluable disease assessment prior to ICE.</i>
	No disease recurrence or death	Treatment policy strategy	All data collected, regardless of any occurrence of this ICE, will be used in the analysis.
Population-level summary	Hazard ratio between the 2 treatment groups		

Sensitivity analyses:

A sensitivity analysis was performed in addition to the primary analysis by censoring events after new anti-cancer therapy (radiation, systemic therapy other than hormonal therapy) at the last disease assessment before new anti-cancer therapy.

A sensitivity analysis for the primary endpoint whereby the first SPT is counted as a DFS event was also performed.

Interim analyses:

Three interim analyses are planned for the primary endpoint of DFS in addition to the final analysis. The interim analyses will be performed when approximately 83 DFS events (50% of total DFS events), 107 DFS events (65% of total DFS events), and 132 DFS events (80%) have been observed. The final analysis of DFS will be performed when approximately 165 DFS events have been observed.

The Lan-DeMets O'Brien-Fleming spending function will be used for type I error control in the analysis of DFS. Table 6 demonstrates an example of alpha spending boundary for DFS analyses. For each interim and final DFS analysis, the alpha spending function will be updated based on actual number of DFS events included in the analysis.

Table 11: Example of alpha spending for analysis of DFS

Analysis	Statistic	Value
Interim Analysis 1 DFS events = ~83	Z	2.9525
	Alpha (2-sided ^a)	0.0032
Interim Analysis 2 DFS events = ~107	Z	2.5833
	Alpha (2-sided ^a)	0.0098
Interim Analysis 3 DFS events = ~132	Z	2.3081
	Alpha (2-sided ^a)	0.0210
Final Analysis DFS events = ~165	Z	2.0331
	Alpha (2-sided ^a)	0.0421

DFS – disease-free survival

Secondary endpoint, definition and censoring:

- Overall survival, defined as time from randomization to the date of death. A patient who has not died will be censored on the last known date as alive.
- Freedom from locoregional recurrence, defined as time from randomization to the date of first locoregional recurrence (LRR). Patients who died without a preceding LRR will be censored on the date of death. For patients who do not have a LRR or death, FFLRR will be censored on the date of last disease assessment.
- Freedom from distant recurrence, defined as time from randomization to the date of first distant recurrence (DR). Patients who died without a preceding DR will be censored on the date of death. For patients who do not have a DR or death, FFDR will be censored on the date of last disease assessment.
- Cumulative occurrence of SPTs for each patient from randomization to occurrence of first primary endpoint event or end of study.

Secondary Efficacy Analysis

Overall survival, FFLRR, and FFDR will be analyzed as follows:

- Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs will be presented for each treatment group. Kaplan-Meier curves will be presented for each treatment group.

- The HR and its 95% CI will be estimated by a stratified Cox Regression model using the treatment group as a covariate and anatomical region of resected high-risk tumor (HN vs non HN) and geographical region (North America vs Australia/New Zealand vs ROW) as stratification factors.

The annualized rates of SPTs and proportion of patients that develop SPTs during the time from randomization to last dose of study drug plus 90 days and during the study period, excluding Part 2 of the study, will be summarized for each treatment group.

The annualized rate of SPTs during the two observation periods defined above will also be analysed using a negative binomial model. The model will include the number of SPTs occurring during the observation period as the response variable, with the treatment group and the two stratification factors used for the primary efficacy endpoint as covariates. The estimated annualized SPT rate for each treatment group and its 2-sided 95% CI will be summarized. The event rate ratio of cemiplimab and placebo will be presented with 2-sided 95% CI.

As regards OS, hypothesis testing will not be performed because 3-year OS in the control group is expected to be $\geq 80\%$.

Control of Multiplicity

The familywise type I error rate for the study is strictly controlled at 2-sided α of 0.05. The type I error rate for interim and final analyses of the primary endpoint of DFS is controlled at a 2-sided α of 0.05 using the O'Brien-Fleming spending function. All secondary endpoints will be summarized descriptively and will not be tested.

Changes from protocol-specified analyses:

Amendment 2: The main elements of this amendment are:

Revisions or clarifications regarding the inclusion criteria (see table below)

Revision of the dosing schedule to Q6W after the initial 12 weeks

Incorporation of interim analyses for the primary endpoint DFS

The following table outlines the changes made with Protocol amendment 2 dated 29 June 2021. There is only one SAP, dated 25 February 2024. The SAP is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses and analysis presentation to be used for the study specified in protocol R2810-ONC-1788, amendment 2 dated 29 Jun 2021.

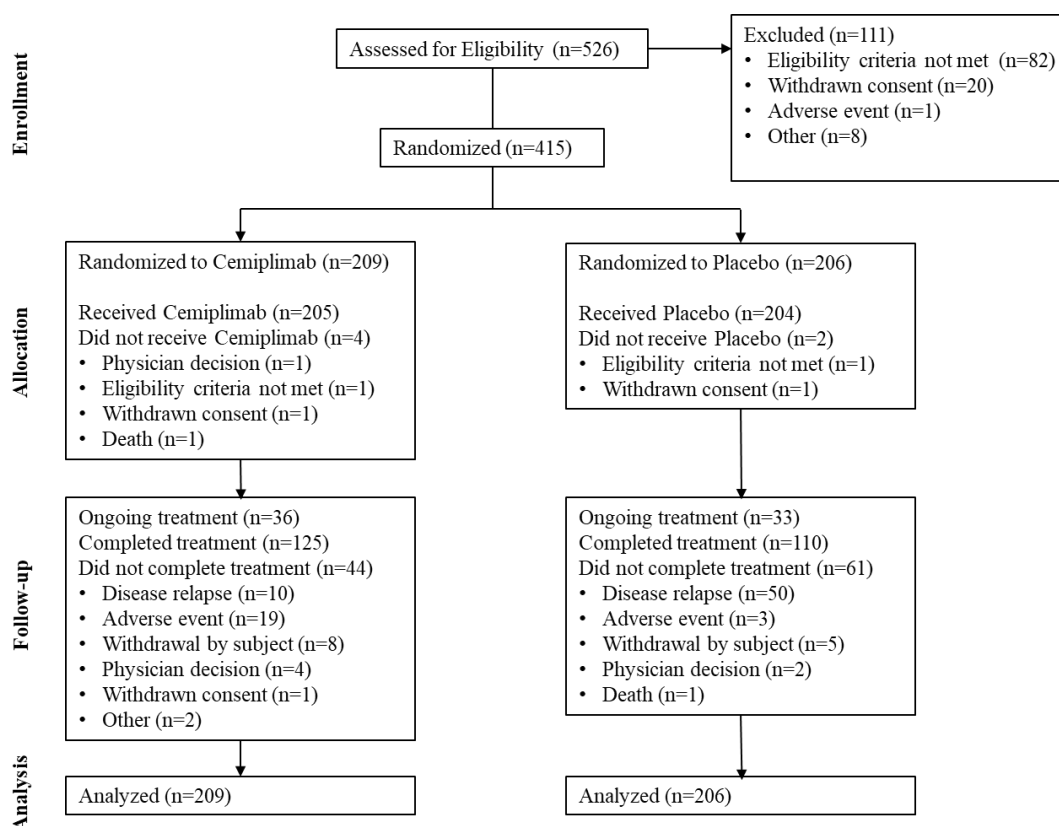
Table 12: Amendments of statistical importance included in Protocol amendment 2

Change	Rationale	Section Changed
The statistical plan has been updated with the addition of interim analyses of the primary endpoint of DFS at approximately 50%, 65% and 80% of the total DFS events (ie, recurrence or any cause death) in addition to the final analysis of DFS.	The addition of interim analyses provides for early efficacy assessment. Consequently, relevant analytical changes for multiplicity adjustment have also been incorporated.	Section 5.1.7 End of Study (EOS) Definition –For the Primary Endpoint Analysis Section 5.2 Planned Interim Analysis Section 10.2 Justification of Sample Size Section 10.4.4.1. Primary Efficacy Analysis Section 10.4.5 Control of Multiplicity (new section) Section 10.5 Interim Analysis
The eligibility criteria have been updated to allow patients with cutaneous squamous cell carcinoma (CSCC) involvement in ≥ 3	To allow the enrolled subjects to include a broader population of patients at high risk of CSCC recurrence. Patients with CSCC involvement in ≥ 3 lymph nodes are	Section 3.2.3 Rationale for Patient Population Section 6.2.1 Inclusion Criteria (criterion #3)

Results

Participant flow

Table 13: Participant flow in Study 1788 (DCO 04 Oct 2024)



Enrolment for the global cohort of study 1788 is complete with 526 patients enrolled in Part 1 of the study. Of the 415 randomized patients, 209 were randomized to the cemiplimab arm, 206 to the placebo group; 205 (98.9%) patients in the cemiplimab arm and 204 (99%) in the placebo group received study treatment. A total of 6 (1.4%) randomized patients did not receive any study treatment.

Table 14: Participant Disposition Part 1 and EOS (Full Analysis Set)

	Cemiplimab (N=209)	Placebo (N=206)	Total (N=415)
Participants randomized but not treated, n (%)	4 (1.9%)	2 (1.0%)	6 (1.4%)
Participants who completed treatment, n (%)	125 (59.8%)	110 (53.4%)	235 (56.6%)
Participants who are ongoing treatment, n (%)	36 (17.2%)	33 (16.0%)	69 (16.6%)
Participants who did not complete treatment, n (%)	44 (21.1%)	61 (29.6%)	105 (25.3%)
Reason for treatment discontinuation, n (%)			
Disease relapse	10 (4.8%)	50 (24.3%)	60 (14.5%)

	Cemiplimab	Placebo	Total
	(N=209)	(N=206)	(N=415)
Adverse event	19 (9.1%)	3 (1.5%)	22 (5.3%)
Withdrawal by subject	8 (3.8%)	5 (2.4%)	13 (3.1%)
Physician decision	4 (1.9%)	2 (1.0%)	6 (1.4%)
Other [1]	2 (1.0%)	0	2 (0.5%)
Death	0	1 (0.5%)	1 (0.2%)
Withdrawal of consent	1 (0.5%)	0	1 (0.2%)
Participants who completed the study, n (%)	0	0	0
Participants who are ongoing in the study, n (%)	187 (89.5%)	175 (85.0%)	362 (87.2%)
Participants who did not complete the study, n (%)	22 (10.5%)	31 (15.0%)	53 (12.8%)
Reason for not completing the study, n (%)			
Death	12 (5.7%)	13 (6.3%)	25 (6.0%)
Withdrawal of consent	2 (1.0%)	9 (4.4%)	11 (2.7%)
Physician decision	2 (1.0%)	2 (1.0%)	4 (1.0%)
Sponsor request	1 (0.5%)	2 (1.0%)	3 (0.7%)
Disease relapse	2 (1.0%)	0	2 (0.5%)
Lost to follow-up	0	2 (1.0%)	2 (0.5%)
Withdrawal by subject	2 (1.0%)	1 (0.5%)	3 (0.7%)
Other [1]	1 (0.5%)	2 (1.0%)	3 (0.7%)

Recruitment

Enrolment for the global cohort is complete with 526 patients screened, 415 patients were randomized in part 1. The first patient was randomized into the study on 04 Jun 2019, and the last patient was randomized on 20 Aug 2024.

A total of 107 sites across **16** countries worldwide randomized at least 1 patient into the global cohort: Australia (28 sites), Brazil (8 sites), Canada (2 sites), EU (38 sites), Japan (4 sites), New Zealand (1 site), Russia (3 sites), UK (5 sites) and USA (18 sites).

As of the data cutoff (DCO) of 04 Oct 2024, the median duration of follow-up (FU) for all patients in the part 1 study was **18.3** months, with median FU of **23.5** months in the cemiplimab arm and **13.2** months in the placebo arm.

The median follow for all patients is 30 months with provided updated data (DCO 07 Apr 2025).

Table 15: Duration of follow-up for all patients in part 1 (FAS) DCO: 04 Oct 2024

	Cemiplimab (N=209)	Placebo (N=206)	Total (N=415)
Duration of Study Follow-up (months)			
n	209	206	415
Mean (SD)	23.68 (15.546)	19.28 (15.849)	21.50 (15.832)
Median	23.49	13.24	18.30
Q1 : Q3	10.25 : 34.07	6.21 : 28.85	7.46 : 32.23
Min : Max	0.2 : 60.6	0.1 : 63.8	0.1 : 63.8
Duration of Study Follow-up, n (%)			
≥6 months	174 (83.3%)	157 (76.2%)	331 (79.8%)
≥12 months	146 (69.9%)	115 (55.8%)	261 (62.9%)
≥18 months	125 (59.8%)	86 (41.7%)	211 (50.8%)
≥24 months	102 (48.8%)	68 (33.0%)	170 (41.0%)
≥30 months	72 (34.4%)	50 (24.3%)	122 (29.4%)
≥36 months	45 (21.5%)	37 (18.0%)	82 (19.8%)
≥42 months	31 (14.8%)	29 (14.1%)	60 (14.5%)
≥48 months	20 (9.6%)	18 (8.7%)	38 (9.2%)
≥54 months	6 (2.9%)	4 (1.9%)	10 (2.4%)
≥60 months	1 (0.5%)	1 (0.5%)	2 (0.5%)
≥66 months	0	0	0

Data cut-off as of October 4, 2024.

Conduct of the study

Relevant protocol amendments:

Table 16: Amendment 2 (29 Jun 2021)

Change	Rationale	Section Changed
The statistical plan has been updated with the addition of interim analyses of the primary endpoint of DFS at approximately 50%, 65% and 80% of the total DFS events (ie, recurrence or any cause death) in addition to the final analysis of DFS.	The addition of interim analyses provides for early efficacy assessment. Consequently, relevant analytical changes for multiplicity adjustment have also been incorporated.	Section 5.1.7 End of Study (EOS) Definition –For the Primary Endpoint Analysis Section 5.2 Planned Interim Analysis Section 10.2 Justification of Sample Size Section 10.4.4.1. Primary Efficacy Analysis Section 10.4.5 Control of Multiplicity (new section) Section 10.5 Interim Analysis
The eligibility criteria have been updated to allow patients with cutaneous squamous cell carcinoma (CSCC) involvement in ≥3	To allow the enrolled subjects to include a broader population of patients at high risk of CSCC recurrence. Patients with CSCC involvement in ≥3 lymph nodes are	Section 3.2.3 Rationale for Patient Population Section 6.2.1 Inclusion Criteria (criterion #3)

lymph nodes to satisfy inclusion 3, high risk CSCC	at a similar risk of CSCC recurrence as the initial patient population.	
The dosing regimen of study drug has been modified from 350 mg Q3W IV for the duration of treatment (48 weeks) to 350 mg Q3W IV for 12 weeks followed by 700 mg Q6W IV for 36 weeks	To reduce <u>the</u> number of study and treatment visits for all study participants, based on the concept that, after 12 weeks of treatment, immune responses can be maintained with a less intensive treatment schedule	Section 1 Introduction Section 3.2.2 Rationale for Dose Selection Section 3.3.2 Risk Section 5.1.3 Assigned Treatment in Part 1 Figure 1 Study Schematic for Part 1 the Study (blinded for primary analysis) Section 7.1 Investigational and Reference Treatments Table 2 Schedule of Events: Screening and Treatment in Part 1 of the Study
Clarified nodal/non-nodal stratification in the case that a patient has both nodal and non-nodal high risk features they should be stratified to the nodal stratum	Clarification to ensure randomization strata are mutually exclusive	Section 3.2.3 Rationale for Patient Population Section 7.4 Method of Treatment Assignment
Added history of CLL (presence or absence) as stratification factor	As the inclusion criteria have been widened to include CLL patients, this has been added to balance patients across treatment groups	Section 7.4 Method of Treatment Assignment Section 10.4.4.1 Primary Efficacy Analysis

Table 17: Number of patients per Protocol Amendment

Protocol version at randomization	Number of patients who signed at randomisation	Number of patients who signed PA2 before End of Treatment (EOT)	Number of patients who did not sign PA2 before End of Treatment (EOT)
Original	23	2	21
PA1	110	50	60
PA2	282	282	0
Total	415	334	81

Table 18: Protocol deviations

	Cemiplimab (N = 209)	Placebo (N = 206)	Total (N = 415)
Number of Important protocol deviations	8	10	18
Participants with any Important protocol deviation, n (%)	8 (3.8%)	10 (4.9%)	18 (4.3%)
Participants with important protocol deviation by type, n (%)			
Entered study even though entry criteria was not satisfied	5 (2.4%)	3 (1.5%)	8 (1.9%)
Inadequate informed consent administration	2 (1.0%)	1 (0.5%)	3 (0.7%)
Other treatment compliance	1 (0.5%)	5 (2.4%)	6 (1.4%)
Received wrong treatment or incorrect dose	0	1 (0.5%)	1 (0.2%)

Note: When calculating percentages, a participant for whom more 2 or more important deviations with the same type is counted only once for that type.

17 patients had 85 minor protocol deviations related to COVID-19 pandemic, the majority related to missed/delayed follow-up procedures (physical examinations, lab tests, imaging and PRO questionnaires).

Baseline data

Table 19: Participant Demographics and Baseline Characteristics (Full Analysis Set)

Characteristics	Cemiplimab (N=209)	Placebo (N=206)	Total (N=415)
Age (years)			
N	209	206	415
Mean (SD)	69.2 (10.35)	69.1 (10.55)	69.2 (10.44)
Median	71.0	70.5	71.0
Q1: Q3	63.0 : 77.0	63.0 : 77.0	63.0 : 77.0
Min: Max	33 : 87	36 : 95	33 : 95
Geographic Region			
North America	37 (17.7%)	31 (15.0%)	68 (16.4%)
Australia/New Zealand	90 (43.1%)	90 (43.7%)	180 (43.4%)
ROW	82 (39.2%)	85 (41.3%)	167 (40.2%)

Characteristics	Cemiplimab (N=209)	Placebo (N=206)	Total (N=415)
Race, n (%)			
White	189 (90.4%)	189 (91.7%)	378 (91.1%)
Asian	5 (2.4%)	8 (3.9%)	13 (3.1%)
Other	1 (0.5%)	1 (0.5%)	2 (0.5%)
Unknown	7 (3.3%)	4 (1.9%)	11 (2.7%)
Not Reported	7 (3.3%)	4 (1.9%)	11 (2.7%)
Sex, n (%)			
Male	174 (83.3%)	174 (84.5%)	348 (83.9%)
Female	35 (16.7%)	32 (15.5%)	67 (16.1%)
ECOG Performance Score, n (%)			
0	133 (63.6%)	131 (63.6%)	264 (63.6%)
1	76 (36.4%)	75 (36.4%)	151 (36.4%)
Tumor Location, n (%)			
HN CSCC	166 (79.4%)	177 (85.9%)	343 (82.7%)
Non-HN CSCC	43 (20.6%)	29 (14.1%)	72 (17.3%)
High Risk Category [a]			
Nodal	125 (59.8%)	117 (56.8%)	242 (58.3%)
Non-Nodal	84 (40.2%)	89 (43.2%)	173 (41.7%)
Stage, n (%) [b]			
Stage I	2 (1.0%)	5 (2.4%)	7 (1.7%)
Stage II	3 (1.4%)	4 (1.9%)	7 (1.7%)
Stage III	53 (25.4%)	52 (25.2%)	105 (25.3%)

Characteristics	Cemiplimab (N=209)	Placebo (N=206)	Total (N=415)
Stage IV	149 (71.3%)	145 (70.4%)	294 (70.8%)
Unknown	2 (1.0%)	0	2 (0.5%)
Patients who received prior systemic therapy for CSCC, n (%)			
1 Regimen	7 (3.3%)	13 (6.3%)	20 (4.8%)
Number of Prior CSCC Cancer-related Surgery, n (%) [c]			
1	9 (4.3%)	5 (2.4%)	14 (3.4%)
2	51 (24.4%)	41 (19.9%)	92 (22.2%)
≥3	149 (71.3%)	160 (77.7%)	309 (74.5%)
Summary of Prior Adjuvant CSCC Radiation Therapy			
Number of participants with prior adjuvant radiotherapy for high risk CSCC, n (%)	209 (100%)	206 (100%)	415 (100%)
Method of Radiotherapy, n (%)			
Intensity-modulated RT	160 (76.6%)	150 (72.8%)	310 (74.7%)
3 Dimensional Conventional RT	27 (12.9%)	28 (13.6%)	55 (13.3%)
Other [d]	23 (11.0%)	29 (14.1%)	52 (12.5%)
Total RT Dose, n (%)			
<50 Gy [e]	5 (2.4%)	3 (1.5%)	8 (1.9%)
50-59 Gy	56 (26.8%)	53 (25.7%)	109 (26.3%)
60-69 Gy	159 (76.1%)	156 (75.7%)	315 (75.9%)
≥70 Gy	1 (0.5%)	1 (0.5%)	2 (0.5%)
Time from Radiation Therapy for high-risk CSCC Completion to Randomization (months) [f]			

Characteristics	Cemiplimab (N=209)	Placebo (N=206)	Total (N=415)
N	208	205	413
Mean (SD)	1.4 (0.49)	1.4 (0.49)	1.4 (0.49)
Median	1.3	1.3	1.3
Q1:Q3	1.1 : 1.8	1.1 : 1.8	1.1 : 1.8
History of CLL, n (%)	2 (1.0%)	2 (1.0%)	4 (1.0%)

[a] Patients with both nodal and non-nodal high-risk criteria are classified as nodal. Nodal high-risk criteria are extracapsular extension and or ≥ 3 involved lymph nodes, regardless of extracapsular extension. Non-nodal high-risk criteria are any of the following: in-transit metastases, T4, PNI, or recurrent + ≥ 1 other additional feature.

[b] Staging was per AJCC eighth edition for HN lesions ([AJCC, 2017](#)) and Union for International Cancer Control ninth edition for non-HN lesions ([UICC, 2015](#)).

[c] A patient may have more than one surgery location. Surgeries include surgeries for the primary high-risk CSC C as well as surgeries for any other prior CSCC.

[d] Details on other RT techniques are provided in PTL 16.2.4.5.

[e] For these patients, BED conversion was ≥ 50 Gy.

[f] Time from Radiation Therapy for High Risk CSCC Completion to Randomization (months) = (Date of randomization – Date of end of radiation therapy for high-risk tumor)/30.4375.

Note on demographic data: There were discrepancies between EDC and IWRS data, and IWRS tables are presented post-text.

Abbreviations: AJCC, American Joint Committee on Cancer; BED, Biologically equivalent dose; CSCC, Cutaneous squamous cell carcinoma; EDC, Electronic data capture (database); Gy, Gray; HN, Head and neck; IWRS, Interactive web response system; PNI, Perineural invasion; ROW, Rest of world; RT, Radiation therapy; SD, Standard deviation.

Table 20: Baseline Disease Characteristics (Full Analysis Set)

	Cemiplimab (N=209)	Placebo (N=206)	Total (N=415)
High Risk Feature			
Nodal Only	98 (46.9%)	97 (47.1%)	195 (47.0%)
Non-Nodal Only	84 (40.2%)	89 (43.2%)	173 (41.7%)
Both Nodal and non-Nodal	27 (12.9%)	20 (9.7%)	47 (11.3%)

Data cut-off as of 4 Oct²⁰ 2024.

Table 21: Outcome of Surgery for High-risk CSCC in Patients with T3 or T4 CSCC

	Cemiplimab (N=209)	Placebo (N=206)
Participants with T3, T4, T4a, and T4b Stage, n (%)	98 (46.9%)	93 (45.1%)

	Cemiplimab (N=209)	Placebo (N=206)
Outcome of Surgery for High Risk CSCC, n (%)		
R0	45 (21.5%)	46 (22.3%)
R1	44 (21.1%)	38 (18.4%)
Not Evaluable	9 (4.3%)	9 (4.4%)

Data cut-off as of 04 Oct 2024

Numbers analysed

Table 22: Analysis Sets (all randomized patients)

	Cemiplimab	Placebo	Total
Full analysis set (FAS)	209	206	415
Safety analysis set (SAF)	205	204	409
Pharmacokinetic analysis set (PKAS)	197	21 [a]	218
Anti-drug antibody analysis set	148	139	287

[a] Prior to unblinding based on IA1, samples from 21 patients receiving placebo were analyzed for cemiplimab concentrations.

Source: PTT 14.1.1.2

Table 23: Analysis Sets by dosing regimen (all randomized patients)

	Q3W Only		Q3W start/Q6W switch	
	Cemiplimab 350 mg	Placebo	Cemiplimab 350/700 mg	Placebo
Full analysis set (FAS) [a]	38	43	171	163
Safety analysis set (SAF) [a]	65	64	140	140
Pharmacokinetic analysis set (PKAS)	59	21 [b]	138	0
Anti-drug antibody analysis set	17	6	131	133

[a] If a patient consented to Q3W/Q6W switch dosing regimen, but did not receive Q6W dose for any reason, they were counted in Q3W dosing regimen in the SAF and were counted in the Q3W/Q6W switch dosing regimen in the FAS.

[b] Prior to unblinding based on IA1, samples from 21 patients receiving placebo were analyzed for cemiplimab concentrations.

Abbreviations: Q3W, Every 3 weeks; Q6W, Every 6 weeks.

Source: PTT 14.2.1.5.1, PTT 14.3.1.1.2, Table 1 in Appendix 16.1.14

Majority of patients switched at Week 12 and some patients due to the timing of protocol amendment switched after Week 12.

Table 11: Patients who Switched from 350 mg Q3W to 700 mg Q6W by Time of Switch (All Randomized Patients)

	Q3W Only (no switch)		Q3W start/Q6W switch at week 12		Q3W start/Q6W switch after week 12	
	Cemiplimab 350 mg	Placebo	Cemiplimab 350/700 mg	Placebo	Cemiplimab 350/700 mg	Placebo
Pharmacokinetic analysis set (PKAS)	59	NA	112	NA	26 [a]	NA

[a] Of the 26 patients who switched from Q3W dosing to Q6W dosing later than week 12, 14 patients switched at week 18, 7 patients at week 24, and 5 patients after week 24.

Abbreviations: NA, Not available; Q3W, Every 3 weeks; Q6W, Every 6 weeks.

Source: Table 7.1.1.02 in Appendix 16.1.14

Outcomes and estimation

Primary endpoint

DFS by INV

Table 24: Summary of Disease-Free Survival (Full Analysis Set)

	Cemiplimab (N=209)	Placebo (N=206)
Disease Free Survival		
Number of DFS events, n (%)	24 (11.5%)	65 (31.6%)
Disease recurrences, n (%)	18 (8.6%)	61 (29.6%)
Deaths, n (%) [a]	6 (2.9%)	4 (1.9%)
Number of censored participants, n (%)	185 (88.5%)	141 (68.4%)
Median DFS (95% CI), (months) [b]	NR (NE, NE)	49.4 (48.5, NE)
Stratified log-rank test p-value [c][d]	<0.0001	
HR (95% CI) [c][e]	0.319 (0.199, 0.511)	
Estimated event-free probability, % (95% CI) [b]		
3 months	95.9 (92.0, 97.9)	90.2 (85.0, 93.6)
6 months	94.3 (89.9, 96.8)	79.9 (73.5, 85.0)
12 months	92.4 (87.5, 95.5)	69.5 (62.1, 75.7)
24 months	87.1 (80.3, 91.6)	64.1 (55.9, 71.1)
36 months	83.1 (74.9, 88.9)	60.4 (51.1, 68.5)
48 months	80.5 (70.5, 87.4)	60.4 (51.1, 68.5)

[a] Only shows Deaths that were counted as DFS events; does not include deaths in patients who previously had recurrence.

[b] Based on Kaplan-Meier method.

[c] Stratified by high-risk tumor location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.

[d] 2-sided nominal p-value. Significance threshold is set to 0.00455 using the O'Brien Fleming alpha spending function.

[e] Based on stratified proportional hazards model (cemiplimab vs placebo).

Abbreviations: CI, Confidence interval; DFS, Disease-free survival; EDC, Electronic data capture; HN, Head and neck; HR, Hazard ratio; N, Number of patients enrolled; NE, Not evaluated; NR, Not reported; ROW, Rest of world.

Updated DFS results:

Table 25: DFS at primary analysis and with approximately 6 months follow-up

	Primary Analysis Data cut 4 Oct 2024		6 month follow up Data cut 7 Apr 2025	
	Cemiplimab (N = 209)	Placebo (N = 206)	Cemiplimab (N = 209)	Placebo (N = 206)
Number of DFS events, n (%)	24 (11.5%)	65 (31.6%)	29 (13.9%)	68 (33.0%)
Disease recurrences, n (%)	18 (8.6%)	61 (29.6%)	22 (10.5%)	64 (31.1%)
Deaths, n (%)	6 (2.9%)	4 (1.9%)	7 (3.3%)	4 (1.9%)
Number of Censored Participants, n (%)	185 (88.5%)	141 (68.4%)	180 (86.1%)	138 (67.0%)
Median DFS, (95% CI, months) [a]	NR (NE, NE)	49.4 (48.5, NE)	NR (NE, NE)	NR (NE, NE)
Stratified log-rank test p-value [b][c]	<0.0001		<0.0001	
HR (95% CI) [b][d]	0.319 (0.199, 0.511)		0.354 (0.229, 0.548)	

[a] Based on Kaplan-Meier method.

[b] Stratified by high-risk tumor (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.

[c] 2-sided p-value. Significance threshold is set to 0.00455 using the OBrien Fleming alpha spending function.

[d] Based on stratified proportional hazards model (cemiplimab vs placebo).

Source: Module 5.3.5.1 R2810-ONC-1788 CSR PTT 14.2.1.1 and Table 14.2.1.1

Table 26: Summary of Participants Censored in Disease Free Survival (Full Analysis Set)

	Cemiplimab (N=209)	Placebo (N=206)
Number of patients without event, n (%)	185 (88.5%)	141 (68.4%)
Reason for censoring, n (%)		
Last Imaging without Recurrence	174 (83.3%)	132 (64.1%)
Randomized and treated - No post baseline disease assessment	8 (3.8%)	7 (3.4%)
Randomized and not Treated- No post baseline Imaging	3 (1.4%)	2 (1.0%)

Data cut-off as of 04 Oct 2024.

Figure 10: Kaplan-Meier curve of DFS (FAS) – 07 Apr 2025

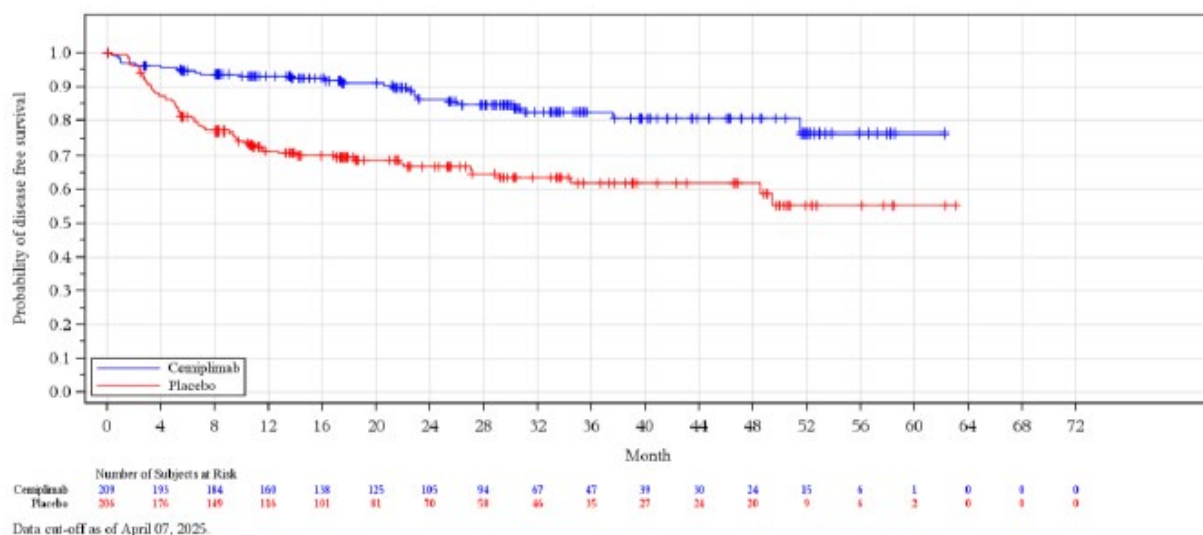


Table 27: Disease Free Survival by Dosing Regimen (Safety Analysis Set)

	Q3W Only		Q3W Start/Q6W Switch ^d	
	Cemiplimab (N=65)	Placebo (N=64)	Cemiplimab (N=140)	Placebo (N=140)
Number of events, n (%)	13 (20.0%)	28 (43.8%)	10 (7.1%)	37 (26.4%)
Disease recurrences, n (%)	11 (16.9%)	27 (42.2%)	7 (5.0%)	34 (24.3%)
Death, n (%)	2 (3.1%)	1 (1.6%)	3 (2.1%)	3 (2.1%)
Number of censored patients, n (%)	52 (80.0%)	36 (56.3%)	130 (92.9%)	103 (73.6%)
Median (95% CI), (months)[a]	NR (NE, NE)	48.5 (5.5, NE)	NR (37.6, NE)	NR (NE, NE)
HR (95% CI) [b][c]	0.436 (0.223, 0.849)		0.202 (0.097, 0.420)	
Estimated Event-Free Probability, % (95% CI) [a]				
3 months	87.5 (75.6, 93.8)	75.3 (61.8, 84.6)	100 (100, 100)	96.2 (91.2, 98.4)
6 months	85.5 (73.1, 92.5)	60.6 (46.5, 72.0)	98.4 (93.9, 99.6)	87.9 (81.0, 92.4)
12 months	83.5 (70.6, 91.1)	56.9 (42.9, 68.7)	96.7 (91.3, 98.7)	74.2 (65.2, 81.2)
24 months	77.1 (63.1, 86.4)	54.9 (40.9, 66.9)	91.6 (82.2, 96.1)	66.7 (56.2, 75.3)
36 months	74.8 (60.3, 84.6)	52.7 (38.6, 64.9)	86.8 (74.7, 93.3)	63.2 (50.8, 73.3)

Data cut-off as of 04 Oct 2024.

[a] Based on Kaplan-Meier method.

[b] Stratified by high-risk tumor (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.

[c] Based on stratified proportional hazards model (cemiplimab vs placebo)

[d] Note This includes patients that switched at week 12 and patients who switched after week 12 dependent on timing of signing the ICF for PA2.

Table 28: Sensitivity analysis of Disease Free Survival by censoring participants with new anti-cancer therapy (Full Analysis Set)

	Cemiplimab (N=209)	Placebo (N=206)
Number of events, n (%)	23 (11.0%)	63 (30.6%)
Disease recurrences, n (%)	17 (8.1%)	61 (29.6%)
Deaths, n (%)	6 (2.9%)	2 (1.0%)
Number of censored participants, n (%)	186 (89.0%)	143 (69.4%)
Median (95% CI), (months)[a]	NR (NE, NE)	NR (48.5, NE)
Stratified log-rank test p-value [b][c]	<0.0001	
HR (95% CI) [b][d]	0.311 (0.192, 0.503)	
Estimated Event-Free Probability, % (95% CI) [a]		
3 months	95.9 (92.0, 97.9)	90.1 (84.9, 93.6)
6 months	94.3 (89.9, 96.8)	79.7 (73.2, 84.8)
12 months	92.4 (87.5, 95.5)	69.2 (61.7, 75.5)
18 months	91.7 (86.5, 94.9)	67.5 (59.9, 74.0)
24 months	87.8 (81.1, 92.2)	64.3 (56.2, 71.4)
30 months	85.3 (77.7, 90.5)	62.9 (54.4, 70.2)
36 months	83.7 (75.5, 89.4)	60.6 (51.1, 68.8)
42 months	81.1 (71.1, 88.0)	60.6 (51.1, 68.8)
48 months	81.1 (71.1, 88.0)	60.6 (51.1, 68.8)
54 months	81.1 (71.1, 88.0)	53.0 (36.1, 67.3)
60 months	NE (NE, NE)	NE (NE, NE)

Data cut-off as of October 4, 2024.

[a] Based on Kaplan-Meier method.

[b] Stratified by high-risk tumor (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.

[c] Two-sided nominal p-value, no multiplicity adjustment.

[d] Based on stratified proportional hazards model (cemiplimab vs placebo).

Table 29: Sensitivity analysis of Disease Free Survival including SPT as an event (Full Analysis Set)

	Cemiplimab (N=209)	Placebo (N=206)
Number of events, n (%)	49 (23.4%)	93 (45.1%)
Disease recurrences, n (%)	14 (6.7%)	55 (26.7%)
Deaths, n (%)	6 (2.9%)	4 (1.9%)
Number of censored participants, n (%)	160 (76.6%)	113 (54.9%)
Median (95% CI), (months)[a]	NR (NE, NE)	21.7 (12.9, 39.2)
Stratified log-rank test p-value [b][c]	<0.0001	
HR (95% CI) [b][c]	0.425 (0.299, 0.603)	

Estimated Event-Free Probability, % (95% CI) [a]		
3 months	91.4 (86.5, 94.6)	85.6 (79.8, 89.8)
6 months	87.5 (81.9, 91.4)	73.2 (66.2, 78.9)
12 months	81.1 (74.5, 86.2)	59.1 (51.4, 66.0)
18 months	77.3 (70.1, 83.0)	52.8 (44.8, 60.2)
24 months	73.4 (65.5, 79.8)	48.7 (40.4, 56.5)
30 months	68.4 (59.4, 75.8)	43.4 (34.5, 51.9)
36 months	68.4 (59.4, 75.8)	41.5 (32.3, 50.4)
42 months	62.5 (50.8, 72.2)	39.3 (29.7, 48.7)
48 months	62.5 (50.8, 72.2)	39.3 (29.7, 48.7)
54 months	62.5 (50.8, 72.2)	33.7 (21.1, 46.7)
60 months	NE (NE, NE)	NE (NE, NE)

Data cut-off as of October 4, 2024.

[a] Based on Kaplan-Meier method.

[b] Stratified by high-risk tumor (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.

[c] Two-sided nominal p-value, no multiplicity adjustment.

[d] Based on stratified proportional hazards model (cemiplimab vs placebo).

Figure 11: Kaplan-Meier curve of sensitivity analysis including SPT as an event (Full Analysis Set)

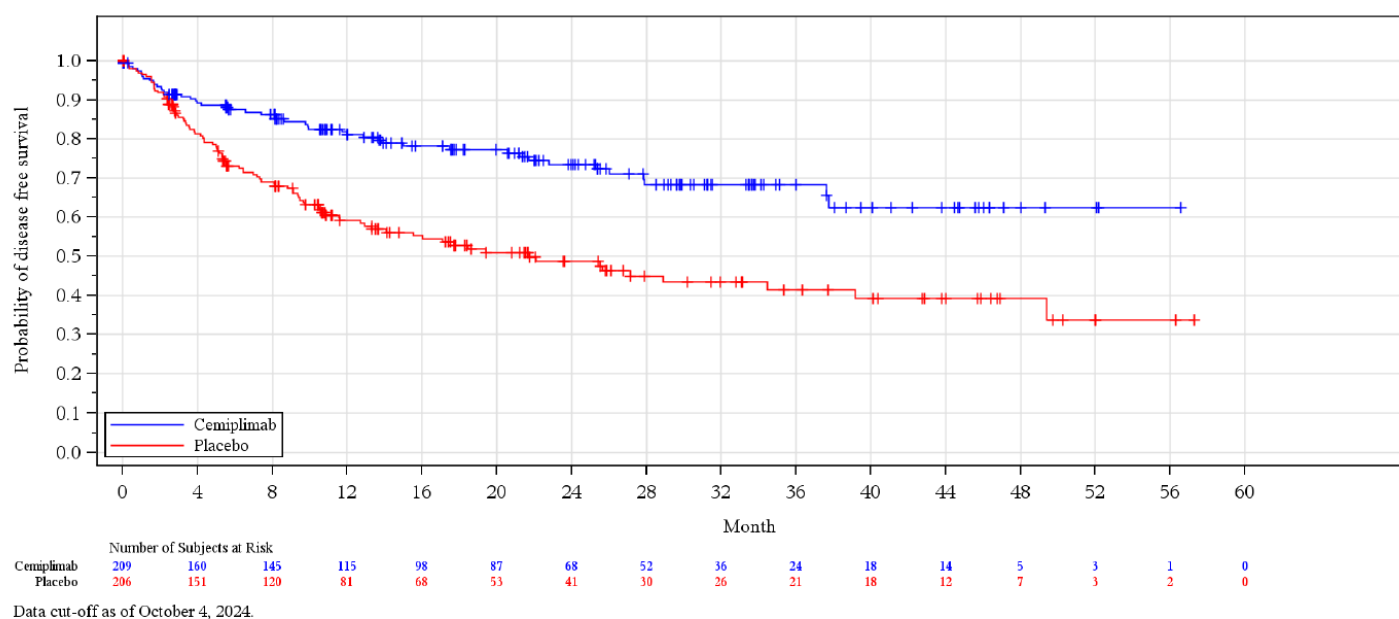


Table 30: Summary of Patterns of Recurrences (Full Analysis Set)

	Cemiplimab (N=209)	Placebo (N=206)
Number of Disease Recurrences, n (%)	18 (8.6%)	61 (29.6%)
Distant Recurrences, n (%) [a]	10 (4.8%)	26 (12.6%)
Distant nodal, n	3	7

	Cemiplimab (N=209)	Placebo (N=206)
Lung, n	3	13
Epidermotropic metastases (EDM), n	2	4
Other distant metastases [b]	3	4
Both distant and Locoregional Recurrence, n [c]	1	5
Locoregional Recurrences, n (%) [d]	8 (3.8%)	35 (17.0%)
Regional nodal, n	2	11
Regional non-nodal/non-skin, n	2	11
In-transit metastases (ITM), n	4	13
Local skin, n [e]	0	2

[a] Total number of patients with distant recurrences is provided in this row. The indented rows below itemize the sites reported for distant recurrences at time of DFS events. The number of itemized distant recurrences in the indented rows is > number of patients with distant recurrences in the top row because some patients had more than one site of distant metastatic disease at the time of disease recurrence.

[b] Other sites of distant metastases at time of DFS were spleen (n=1), bone (n=4), brain (n=1), other soft tissue (n=1), and pleura (n=1).

[c] 6 patients had both distant and locoregional disease at time of recurrence, and are counted as distant (1 patient in cemiplimab arm, 5 patients in placebo arm): 2 patients had distant lung and locoregional non-nodal non-skin recurrences; 1 patient had distant nodal and locoregional nodal recurrences; 1 patient had distant lung and locoregional ITM recurrences; 1 patient had distant lung, distant nodal, distant bone, and locoregional ITM recurrences; and 1 patient had distant lung and locoregional nodal recurrences.

[d] Total number of patients with LRRs is provided in this row. The indented rows below itemize the sites reported for LRRs at time of DFS events. The number of itemized LRRs in the indented rows is > number of patients with LRRs in the top row because some patients had more than one site of LRR disease at the time of disease recurrence.

[e] Disease recurrence at skin at the location of high-risk tumor.

Abbreviations: DFS, Disease-free survival; FAS, Full analysis set; ITM, In-transit metastases; LLR, Locoregional recurrence; N, Number of patients with recurrences.

Table 31: Subsequent therapy for CSCC recurrence (Full Analysis Set - Participants with Recurrence)

	Cemiplimab (N=209)	Placebo (N=206)
Number of participants with recurrence, n participants (%) [a]	18 (8.6%)	61 (29.6%)
Number of participants who received ≥ 1 Line of Systemic Therapy, n participants (%)	10 (4.8%) [b]	51 (24.8%) [c]
Cemiplimab, n participants (%)	5 (2.4%) [d]	51 (24.8%) [e]
Other, n participants (%)	6 (2.9%) [f]	6 (2.9%) [g]
Number of participants who received Radiation Therapy, n participants (%)	5 (2.4%)	7 (3.4%)
Number of participants who had Surgery, n participants (%)	4 (1.9%)	11 (5.3%)

[a] The total number of recurrences is provided in this row. The number of interventions (systemic therapy, surgery, radiation) for recurrent CSCC in the rows below sums to more than the total number of recurrences, because some patients received more than 1 intervention for recurrent CSCC.

[b] The top row indicates 10 patients received systemic therapy for recurrent disease. The indented rows below sum to 11 because 1 patient received cemiplimab and another line of 5-Fluorouracil (5-FU).

[c] The top row indicates 51 patients received systemic therapy for recurrent disease. The indented rows below sum to 57 because several patients received more than 1 line of systemic therapy.

[d] This includes 3 patients who received cemiplimab in Part 2 and 2 patients who received cemiplimab outside of Part 2 for recurrent disease as part of standard of care.

[e] This includes 46 patients who received cemiplimab in Part 2 and 5 patients who received cemiplimab outside of Part 2 for recurrent disease as part of standard of care. 2 patients who received cemiplimab both in Part 2 and outside of Part 2 are counted as having received cemiplimab in Part 2.

[f] The following systemic therapies were reported in the cemiplimab arm in 6 patients: 5-FU single agent (n=1), carboplatin + paclitaxel (n=1), 5-FU + cisplatin (n=1), protein kinase inhibitor (n=1), cetuximab single agent (n=1) and 1 patient received 3 lines of therapy (cetuximab + paclitaxel and cetuximab + docetaxel twice).

[g] The following systemic therapies were reported in the placebo arm in 6 patients: carboplatin + paclitaxel (n=2), cetuximab single agent (n=2), carboplatin + 5-FU + cetuximab (n=1) and 1 patient received 2 lines of chemotherapy (cisplatin + 5-FU doublet and carboplatin single agent). Note that 1 patient received cemiplimab twice (in Part 2 and as standard of care) and carboplatin + paclitaxel.

Abbreviation: 5-FU, 5-Fluorouracil; CSCC, Cutaneous squamous cell carcinoma

Table 32: Sensitivity Analysis of DFS Including New Anti-Cancer Therapy and TEAE Leading to Discontinuation as Events (Full Analysis Set)

	Cemiplimab (N=209)	Placebo (N=206)
Number of events, n (%)	45 (21.5%)	70 (34.0%)
Disease recurrences, n (%)	16 (7.7%)	61 (29.6%)
Deaths, n (%)	5 (2.4%)	2 (1.0%)
Initiation of New Anti-Cancer Therapy, n (%)	4 (1.9%)	4 (1.9%)
TEAE Leading to Treatment Discontinuation, n (%)	20 (9.6%)	3 (1.5%)
Number of censored participants, n (%)	164 (78.5%)	136 (66.0%)
Median (95% CI), (months)[a]	NR (NE, NE)	48.5 (34.5, NE)
HR (95% CI) [b][c]	0.596 (0.409, 0.870)	

Data cut-off as of 04 Oct 2024.

[a] Based on Kaplan-Meier method.

[b] Stratified by high-risk tumor (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.

[c] Based on stratified proportional hazards model (cemiplimab vs placebo).

Secondary endpoints

Freedom from Locoregional Recurrence

Table 33: Summary of Locoregional Recurrence (FFLRR) – Full Analysis Set

	IA1 DCO 04 Oct 2024		IA1 DCO 7 Apr 2025	
	Cemiplimab (N=209)	Placebo (N=206)	Cemiplimab (N=209)	Placebo (N=206)
Locoregional recurrence (FFLRR)				
Number of events, n (%)	9 (4.3%)	40 (19.4%)	11 (5.3%)	42 (20.4%)
Number of censored patients, n (%)	200 (95.7%)	166 (80.6%)	198 (94.7%)	164 (79.6%)
Median (95% CI), (months) [a]	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)
HR (95% CI) [b] [c]	0.195 (0.094, 0.402)		0.222 (0.114, 0.433)	

IA1 DCO 04 Oct 2024			IA1 DCO 7 Apr 2025	
	Cemiplimab (N=209)	Placebo (N=206)	Cemiplimab (N=209)	Placebo (N=206)
Estimated Event-Free Probability, % (95% CI) [a]				
3 months	98.4 (95.3, 99.5)	92.2 (87.4, 95.2)	98.5 (95.5, 99.5)	92.6 (88.0, 95.4)
6 months	98.4 (95.3, 99.5)	85.5 (79.6, 89.8)	98.5 (95.5, 99.5)	86.5 (80.9, 90.5)
12 months	96.6 (92.5, 98.5)	79.1 (72.2, 84.4)	96.9 (93.3, 98.6)	80.2 (73.8, 85.2)
24 months	94.6 (89.1, 97.3)	76.7 (69.1, 82.6)	94.5 (89.4, 97.1)	78.3 (71.4, 83.7)
36 months	92.9 (85.8, 96.5)	74.1 (64.7, 81.3)	91.9 (85.3, 95.7)	75.1 (66.7, 81.6)

[a] Based on Kaplan-Meier method.

[b] Stratified by high-risk tumor location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC

[c] Based on stratified proportional hazards model (cemiplimab vs placebo).

Abbreviations: CI, Confidence interval; EDC, Electronic data capture; FFLRR, Freedom from locoregional recurrence; HN, Head and neck; HR, Hazard ratio; NE, Not evaluated; NR, Not reached; ROW, Rest of world.

Freedom From Distant Recurrence

Table 34: Freedom from Distant Recurrence (Full Analysis Set)

IA1 DCO 04 Oct 2024			DCO 07 Apr 2025	
	Cemiplimab (N=209)	Placebo (N=206)	Cemiplimab (N=209)	Placebo (N=206)
Distant Recurrence (FFDR)				
Number of events, n (%)	10 (4.8%)	26 (12.6%)	12 (5.7%)	28 (13.6%)
Number of censored patients, n (%)	199 (95.2%)	180 (87.4%)	197 (94.3%)	178 (86.4%)
Median (95% CI), (months) [a]	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)
HR (95% CI) [b] [c]	0.346 (0.167, 0.720)		0.374 (0.190, 0.738)	
Estimated Event-Free Probability, % (95% CI) ^a				
3 months	98.0 (94.7, 99.2)	96.9 (93.2, 98.6)	98.0 (94.9, 99.3)	97.0 (93.5, 98.6)

	IA1 DCO 04 Oct 2024		DCO 07 Apr 2025	
	Cemiplimab (N=209)	Placebo (N=206)	Cemiplimab (N=209)	Placebo (N=206)
6 months	96.3 (92.3, 98.2)	92.8 (87.9, 95.8)	96.5 (92.9, 98.3)	93.3 (88.8, 96.1)
12 months	96.3 (92.3, 98.2)	86.2 (79.6, 90.7)	96.5 (92.9, 98.3)	87.7 (81.9, 91.8)
24 months	94.3 (89.0, 97.1)	83.8 (76.3, 89.0)	93.4 (88.1, 96.3)	85.7 (79.2, 90.3)
36 months	94.3 (89.0, 97.1)	81.9 (73.6, 87.9)	93.4 (88.1, 96.3)	81.5 (73.2, 87.4)

[a] Based on Kaplan-Meier method.

[b] Stratified by high-risk tumor location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC

[c] Based on stratified proportional hazards model (cemiplimab vs placebo).

Abbreviations: CI, Confidence interval; EDC, Electronic data capture; FFDR, Freedom from distance recurrence; HN, Head and neck; HR, Hazard ratio; NE, Not evaluated; NR, Not reached; ROW, Rest of world.

Second Primary CSCC Tumors in Part 1 of the Study

Table 35: Annualized SPT Rate During Study Period (Full Analysis Set)

	DCO 04 Oct 2024		DCO 07 Apr 2025	
	Cemiplimab (N = 209)	Placebo (N = 206)	Cemiplimab (N = 209)	Placebo (N = 206)
Number of Patients with at least 1 SPT, n (%)	31 (14.8%)	37 (18.0%)	37 (17.7%)	42 (20.4%)
Patients by number of SPT, n (%)				
1	17 (8.1%)	25 (12.1%)	21 (10.0%)	27 (13.1%)
2	6 (2.9%)	4 (1.9%)	5 (2.4%)	6 (2.9%)
3	2 (1.0%)	1 (0.5%)	4 (1.9%)	2 (1.0%)
4	1 (0.5%)	2 (1.0%)	1 (0.5%)	2 (1.0%)
5	4 (1.9%)	0	4 (1.9%)	0
6	0	1 (0.5%)	1 (0.5%)	1 (0.5%)
7	0	2 (1.0%)	0	2 (1.0%)
9	1 (0.5%)	0	0	0
11	0	0	1 (0.5%)	0
16	0	1 (0.5%)	0	1 (0.5%)
43	0	1 (0.5%)	0	1 (0.5%)
Location of SPT				
Head and Neck	21 (10.0%)	33 (16.0%)	26 (12.4%)	38 (18.4%)
Non-Head and Neck	15 (7.2%)	12 (5.8%)	18 (8.6%)	13 (6.3%)
Total number of SPTs	68	123	84	132
Total patient – years followed	412.4	331.0	503.9	399.1
Unadjusted SPT rate [1]	0.2	0.4	0.2	0.3
Adjusted annualized SPT rate [2] (95% CI)	0.633 (0.361,1.110)	1.202 (0.592,2.442)	0.594 (0.354,0.997)	0.987 (0.522,1.867)

[1] The total number of SPT that occurred during study period divided by the total number of patient-years followed.

[2] Derived using negative binomial model with the total number of SPTs during study period as the response variable, with the treatment arm, anatomical region of resected high-risk tumor (HN vs non-HN), and geographical region (North America vs Australia/New Zealand vs ROW) as covariate, and log-transformed standardized observation duration as an offset variable.

Abbreviations: CI, Confidence interval; HN, Head and neck; ROW, Rest of world; SPT, Second primary CSCC tumor

Overall survival

Table 36: Overall Survival (Full Analysis Set)

	IA1 DCO 04 Oct 2024		DCO 07 APR 2025	
	Cemiplimab (N=209)	Placebo (N=206)	Cemiplimab (N=209)	Placebo (N=206)
Number of deaths, n (%)	12 (5.7%)	13 (6.3%)	15 (7.2%)	18 (8.7%)
Number of censored patients, n (%)	197 (94.3%)	193 (93.7%)	194 (92.8%)	188(91.3%)
Median (95% CI), (months) [a]	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)
HR (95% CI) [b][c]	0.863 (0.391, 1.904)		0.782 (0.392, 1.557)	
Estimated Survival Probability, % (95% CI)[a]				
6 months	98.5 (95.3, 99.5)	99.5 (96.4, 99.9)	98.5 (95.5, 99.5)	99.5 (96.5, 99.9)
12 months	97.9 (94.4, 99.2)	98.3 (94.8, 99.5)	98.0 (94.8, 99.3)	98.0 (94.7, 99.2)
24 months	94.8 (89.6, 97.4)	92.3 (86.5, 95.7)	93.9 (88.9, 96.7)	90.4 (84.7, 94.0)
36 months	89.9 (82.1, 94.4)	92.3 (86.5, 95.7)	90.3 (83.8, 94.3)	90.4 (84.7, 94.0)

[a] Based on Kaplan-Meier method.

[b] Stratified by high-risk tumor location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC

[c] Based on stratified proportional hazards model (cemiplimab vs placebo).

Abbreviations: CI, confidence interval; EDC, electronic data capture; HN, head and neck; HR, hazard ratio; ROW, rest of world.

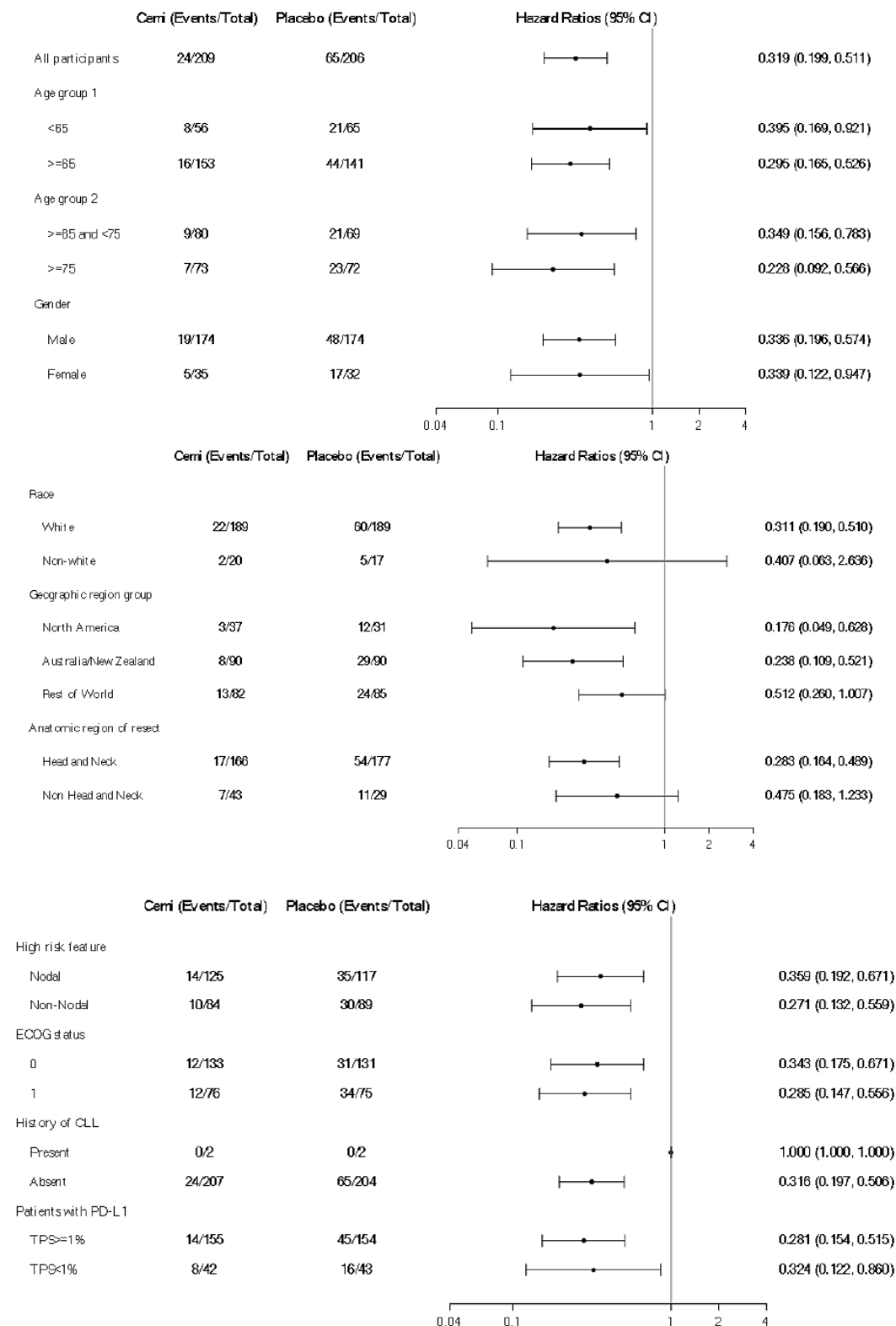
Table 37: Summary of Deaths (Full Analysis Set) DCO 04 Oct 2024

	Cemiplimab (N=209)	Placebo (N=206)
Number of deaths, n (%)	12 (5.7%)	13 (6.3%)
Primary cause of death		
Progression/recurrence of disease	4 (1.9%)	8 (3.9%)
Adverse event	3 (1.4%)	4 (1.9%)
Other	5 (2.4%)	1 (0.5%)

Ancillary analyses

Subgroup analyses

Table 38: Forest Plot for Disease-Free Survival in subgroups (FAS)



Abbreviations: Cemiplimab, Cemiplimab; CI, Confidence interval; CLL, Chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology group; PD-L1, Programmed death ligand-1; TPS, Tumor proportion score

Updated results with additional 6 months follow-up:

Table 39: Disease-Free Survival (FAS) DCO 07 April 2025**Table 2: Disease Free Survival by Subgroup (Full Analysis Set); Updated DCO 07Apr 2025**

	Cemiplimab (N=209)		Placebo (N=206)		HR (95% CI) [b]
	Event (%)	Median Time (95% CI)[a]	Event (%)	Median Time (95% CI)[a]	
All participants	29/209 (13.9%)	NR (NE, NE)	68/206 (33.0%)	NR (48.5, NE)	0.354 (0.229, 0.548)
Age group 1					
<65	9/56 (16.1%)	NR (NE, NE)	22/65 (33.8%)	NR (27.0, NE)	0.423 (0.191, 0.936)
>=65	20/153 (13.1%)	NR (NE, NE)	46/141 (32.6%)	NR (48.5, NE)	0.326 (0.190, 0.560)
Age group 2					
<65	9/56 (16.1%)	NR (NE, NE)	22/65 (33.8%)	NR (27.0, NE)	0.423 (0.191, 0.936)
>=65 and <75	12/80 (15.0%)	NR (NE, NE)	21/69 (30.4%)	NR (34.5, NE)	0.462 (0.223, 0.959)
>=75	8/73 (11.0%)	NR (51.5, NE)	25/72 (34.7%)	NR (29.2, NE)	0.207 (0.084, 0.510)
Gender					
Male	23/174 (13.2%)	NR (NE, NE)	51/174 (29.3%)	NR (48.5, NE)	0.375 (0.229, 0.617)
Female	6/35 (17.1%)	NR (NE, NE)	17/32 (53.1%)	14.1 (5.3, NE)	0.316 (0.122, 0.817)
Race					
White	26/189 (13.8%)	NR (NE, NE)	62/189 (32.8%)	NR (48.5, NE)	0.347 (0.219, 0.552)
Non-white [e]	3/20 (15.0%)	NR (30.8, NE)	6/17 (35.3%)	NR (6.4, NE)	0.388 (0.071, 2.116)
Geographic region group					
North America	4/37 (10.8%)	NR (51.5, NE)	12/31 (38.7%)	49.4 (7.0, NE)	0.222 (0.071, 0.699)[c]
Australia/New Zealand	9/90 (10.0%)	NR (NE, NE)	30/90 (33.3%)	NR (34.5, NE)	0.245 (0.116, 0.517)[c]
Rest of World	16/82 (19.5%)	NR (NE, NE)	26/85 (30.6%)	NR (NE, NE)	0.564 (0.302, 1.054)[c]
Anatomic region of resected high-risk tumor					
Head and Neck	22/166 (13.3%)	NR (NE, NE)	57/177 (32.2%)	NR (48.5, NE)	0.335 (0.204, 0.549)[d]

In vitro biomarker test for patient selection for efficacy

Table 40: Baseline PD-L1 status per TPS (FAS) (DCO 4 Oct 2024)

	Cemiplimab (N=209)	Placebo (N=206)	Total (N=415)
Without PD-L1	12 (5.7%)	9 (4.4%)	21 (5.1%)
With PD-L1	197 (94.3%)	197 (95.6%)	394 (94.9%)
TPS>=1%	155 (74.2%)	154 (74.8%)	309 (74.5%)
TPS<1%	42 (20.1%)	43 (20.9%)	85 (20.5%)

Table 41: Disease-Free Survival by PD-L1 Expression (Full Analysis Set)

	Cemiplimab (N=209)		Placebo (N=206)		HR (95% CI) [b]
	Event (%)	Median Time (95% CI) [a]	Event (%)	Median Time (95% CI) [a]	
All participants	24/209 (11.5%)	NR (NE, NE)	65/206 (31.6%)	49.4 (48.5, NE)	0.319 (0.199, 0.511)
Patients with PD-L1					
TPS ≥1%	14/155 (9.0%)	NR (NE, NE)	45/154 (29.2%)	49.4 (48.5, NE)	0.281 (0.154, 0.515)

	Cemiplimab (N=209)		Placebo (N=206)		
	Event (%)	Median Time (95% CI) [a]	Event (%)	Median Time (95% CI) [a]	HR (95% CI) [b]
TPS <1%	8/42 (19.0%)	NR (37.6, NE)	16/43 (37.2%)	27.1 (14.1, NE)	0.324 (0.122, 0.860)

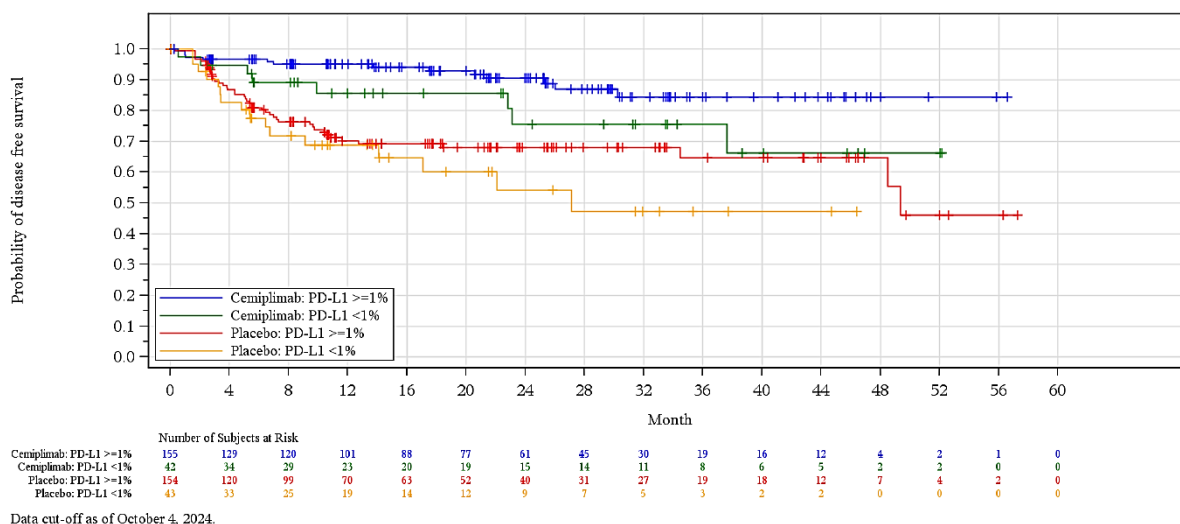
[a] Based on Kaplan-Meier method.

[b] Based on high-risk tumor location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC stratified proportional hazards model (cemiplimab vs placebo).

Note: Subgroup analysis was based on EDC.

Abbreviations: CI, Confidence interval; EDC, Electronic data capture (database); HN, Head and neck; HR, Hazard ratio; N, Number of patients enrolled; NE, Not established; NR, Not reached; PD-L1, Programmed death ligand-1; ROW, Rest of world; TPS, Tumor proportion score.

Figure 12: Kaplan-Meier curve of DFS by PD-L1 (FAS)



Patient-Reported Outcomes in Part 1 of the Study

Table 42: Summary of Overall Change from Baseline in the EORTC QLQ-C30 GHS/QoL, and EQ-5D-3L VAS Scores Within and Between Treatment Arms (FAS) – Part 1

	Cemiplimab (N=164) [a]		Placebo (N=163) [a]		Cemiplimab vs Placebo	
PRO Scale	Baseline Score (observed): Mean (SD)	Change from Baseline: LS Mean (SE), [95% CI]	Baseline Score (observed): Mean (SD)	Change from Baseline: LS Mean (SE), [95% CI]	Observed Difference in LS Mean change	Diff. in Mean Change [b] [95% CI]

EORTC QLQ-C30	75.39	-1.95 (1.18), [-	75.75	-1.02 (1.22),	-0.83	-0.94 [-3.65,
GHS/QoL	(17.48)	4.27, 0.36]	(17.44)	[-3.42, 1.39]		1.77]
EQ-5D-3L VAS	80.13	0.16 (1.03), [-	78.71	0.61 (1.07), [-	-0.65	-0.45 [-2.85,
	(13.96)	1.86, 2.18]	(16.43)	1.51, 2.72]		1.94]

[a] N is the number of subjects with a baseline and at least one post-baseline PRO score.

[b] Estimates are based on a mixed model repeated measures treating time categorical: Change=Treatment arm + Time + Baseline PRO Value + Anatomic region of resected high-risk tumor + Geographic Region + Time*Baseline PRO Value +Time Point*Treatment arm.

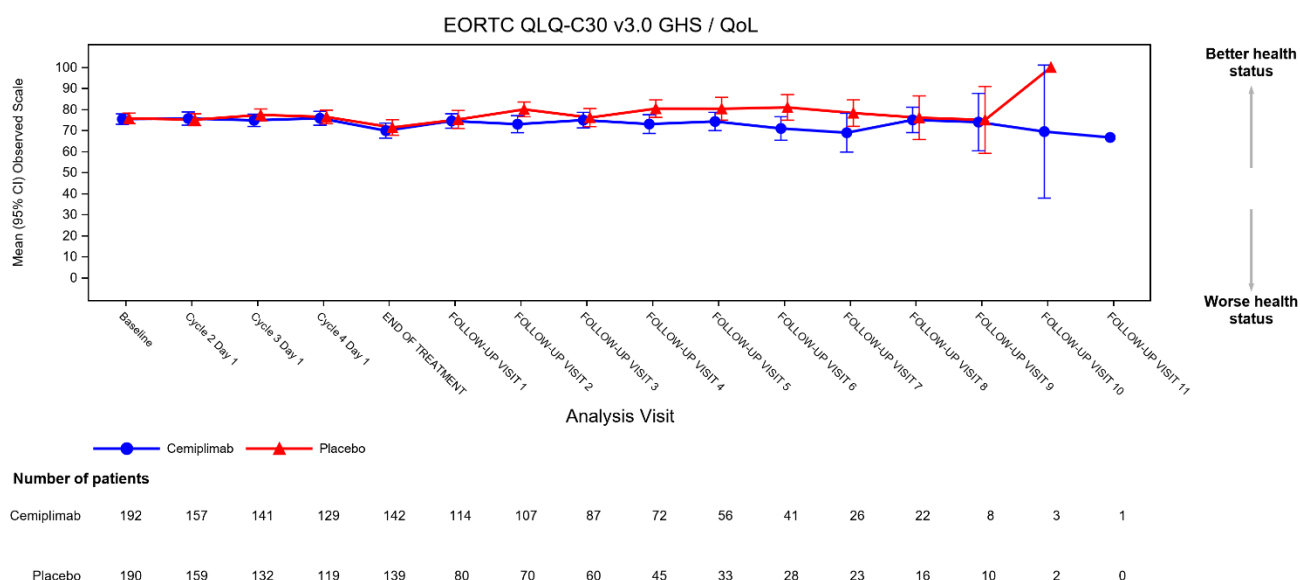
Note: A positive change from baseline value in the EORTC QLQ-C30 GHS/QoL and the EQ-5D-3L VAS indicates improvement.

Note: The model assumed an unstructured covariance among the within subject repeated measurement.

Note: The change from baseline analysis includes only regular cycle visits, including cycles 2 through 4.

Abbreviations: CI, Confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EF, Emotional function; FA, Fatigue; GHS, Global Health Score; LS, least-squares; PA, Pain; PF, Physical functioning; QoL, Quality of life; RF, Role functioning; SD, Standard deviation; SE, Standard error; SMD, Standardized mean difference, VAS, Visual analog scale.

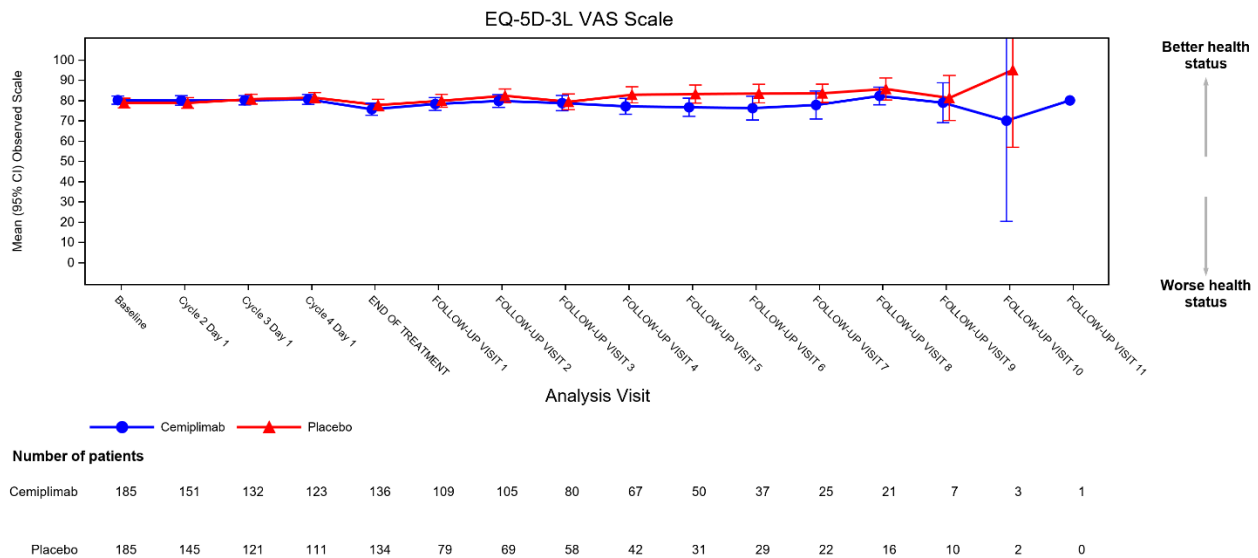
Figure 13: Mean Score Over Time -- EORTC QLQ-C30 GHS/QoL Scale



Note: The 95% CI is truncated if it exceeds the instrument's theoretical range.

Abbreviations: CI, Confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; GHS, Global Health Status; QoL, Quality of life.

Figure 14: Mean Score Over Time - EQ-5D-3L VAS Scale



Note: The 95% CI is truncated if it exceeds the instrument's theoretical range.

Abbreviations: CI, Confidence interval; EQ-5D-3L: EuroQol-5 Dimensions-3 Levels; VAS, Visual analog scale.

Special populations

Table 43: Number of patients per age group in study 1788

	Controlled Trials	Non-controlled trials
Older patients; Age 65-74 (Subjects number /total number)	149/415	n/a
Age 75-84 (Subjects number /total number)	130/415	n/a
Age 85+ (Subjects number /total number)	15/415	n/a

2.4.3. Discussion on clinical efficacy

Cemiplimab (Libtayo) is an anti-PD-1 antibody already approved as monotherapy or in combination for different cancers, mostly in the advanced setting. Based on results from the pivotal trial study 1788, the MAH is seeking the following extension of indication:

Libtayo (cemiplimab) as monotherapy is indicated for the adjuvant treatment of adult patients with CSCC at high risk of recurrence after surgery and radiation.

Design and conduct of clinical studies

The evidence of efficacy pertinent to the proposed indication is solely based on study 1788: an ongoing, Phase III, randomized, double-blind, placebo-controlled, 2-arm, multi-center study which aimed to assess the efficacy and safety of cemiplimab compared to placebo as adjuvant treatment for patients with CSCC at a high-risk of recurrence after surgery and RT. In the event of recurrence,

patients from both arms were allowed to continue cemiplimab in the optional, open-label part 2 of the study. Optional subsequent treatment with cemiplimab, for up to 96 weeks, was allowed for patients on the cemiplimab arm who experience disease recurrence ≥ 3 months after completing 48 weeks of planned cemiplimab treatment.

The design of the study was discussed in the 2019 scientific advice (EMA/H/SA/3225/6/2018/II), which was generally followed. The main issue pointed out by the CHMP was that the MAH planned to perform time-dependent DFS analysis with prespecified number of events, which would not inform about curability of the disease but delay in relapse. Fixed-time endpoint analysis when the risk of relapse is expected to be low in both arms (around three years) was recommended, as the goal of therapy in this setting is to increase cure rate and it would be expected that nearly 50% study population would never relapse after radical primary local treatment. This would lead to exposing some patients to unnecessary risk of toxicity without any potential benefit. The MAH maintained their initially proposed methodology, which includes an event-driven DFS approach, incorporation of the initially proposed stratification factors, and the exclusion of new SCC lesions as events in the DFS analysis.

The in- and exclusion criteria from 1788 study are generally considered adequate and reflect the target population at high risk of recurrence of CSCC after surgery and RT for treatment with cemiplimab. Patients received cemiplimab at the approved dose of 350 mg or placebo every 3 weeks. With the protocol amendment 2, the switch regime (cemiplimab 350mg Q3W for 12 weeks/ 700mg Q6W for additional 36 weeks) was introduced. The justification for the switch was based on convenience for patients and providers and results of PopPK model, the updated model (incorporating covariate for Study 1788), and the observed data from Study 1788, which is considered acceptable. The duration of treatment in both arms was about 1 year (48 weeks). This was based on the literature indicating that the highest risk of CSCC recurrence occurs within the first year. Therefore, cemiplimab was given for the one-year duration to minimize the risk of recurrence. This is agreed; however, it should be noted that the risk of recurrence remains elevated during the first three years, only reaching a plateau thereafter. The proposed wording of the applied indication sufficiently reflects the study population of Study 1788.

Statistical methods: The primary objective of the study was to compare DFS (disease free survival) of patients with high-risk CSCC treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT. The primary endpoint is considered as clinically relevant in the targeted population and endorsed. The use of investigator-assessed only and not employing the RECIST criteria in the assessment is not fully understood, as it can potentially lead to inconsistencies and subjective judgments. This lack of standardization introduces the risk of bias, potentially affecting the reliability and comparability of the results. However, the use of double-blinding and the requirement for biopsy in cases of new lesions help mitigate potential investigator bias. The randomization (1:1) was stratified on the factors: "Anatomic region of resected high-risk tumor", "Geographic Region", "High risk feature", "ECOG PS" and "History of CLL". Of note, "High risk feature", "ECOG PS" and "History of CLL" were not included in the primary analysis and used for balancing treatment only. These stratification factors were accepted at (EMA/H/SA/3225/6/2018/II).

Blinding: Study patient, the principal investigators, and study site personnel were blinded to all randomization assignments throughout the study. Of note, the blinding is maintained after the primary analysis (IA1) which allows for subsequent analyses to establish long-term trajectory of the treatment. This is endorsed.

Upon request, the MAH provided a table of concordance between investigator assessment and IRC assessment. However, as this table was based only on 64 (app. 15%) randomly selected patients and from the FAS, questions regarding the quality of investigator assessment persist.

In particular, the risk of investigator bias cannot be entirely eliminated due to the observed skin toxicity in the experimental arm, where approximately one third of the patients experienced rash.

Efficacy analyses were conducted on the full analysis set (FAS) based on all randomized patients and the treatment allocated (as randomized).

Time to event endpoints, i.e., primary endpoint, Disease free survival (DFS) and secondary endpoints: Overall survival (OS), Freedom from locoregional recurrence (FFLRR), Freedom from distant recurrence (FFDR) were treated by standard survival analysis methods. The primary (DFS) hypothesis was tested by a two-sided (stratified) log rank test. Secondary endpoint: Cumulative occurrence of Second primary CSCC tumours (SPTs) was treated descriptively, i.e. by means of annualized rates of SPTs and proportion of patients that develop SPTs during the time from randomization to last dose of study drug plus 90 days and during the study period, excluding Part 2 of the study. These were summarized for each treatment group.

The present application is based on the first of three planned interim analyses (IA1). Lan-DeMets O'Brien-Fleming spending function was used for type 1 error control. While the control of type 1 error at interim analysis (IA1) is statistically acceptable (given a clarification of threshold calculations), concerns remain regarding maturity of data.

Secondary endpoints were not multiplicity adjusted for type 1 error and are only considered supportive. An update on OS approximately 2 years after the primary analysis (165 DFS events, final analysis) is planned.

There were two amendments of the protocol during the study. Of special statistical importance is the planning of three interim analyses of the primary endpoint, DFS. These were added at the second amendment to the protocol dated 29 June 2021.

Study conduct: Of 526 enrolled patients, 111 patients were screening failures (21.1%). The most common reasons for screening failures were not meeting the eligibility criteria (73.9%) and withdrawal of IC (18%). A very low number of patients (4 patients in the experimental vs. 2 in the placebo arm) did not receive the allocated treatment. The original protocol of 1788 study was amended 2 times. The most relevant amendment (Amendment 2, June 2021) introduced the SWITCH regime (350mgQ3W/700mgQ6W), updated multiple sections of SAP (i.e three event-based IA were added) and some updates to the eligibility criteria (i.e. addition of CLL, ≥ 3 lymph nodes involved to the stratification factors). The MAH justifies changes to SAP that the interim analyses would allow for early efficacy assessments. Approximately 32% (133 patients out of 415) of study population was enrolled before the amendment 2 implementation, 52 had subsequently reconsented before the end of treatment to this amendment and 81 patients were treated according to the previous protocol versions. Overall, issues related to the protocol amendments are acceptable and will not be pursued further. Important protocol deviations were uncommon (<5%) and nearly balanced between arms.

The demographic and clinical characteristics of the patients at baseline were generally balanced in both arms of study 1788 and are considered representative of the overall patient population with CSCC in Europe. The median age was 71 years (range, 33 to 87). 83% of the patients were men and white (90%). About 43% of patients were recruited in Australia/New Zealand, 40% in ROW (EU, UK, Japan, Brazil and Russia), and 16% in North America. The majority of patients (64%) had ECOG PS 0. 83% of tumors were localized in the HN region. Most patients had stage IV (71%) or stage III (25%) according

to AJCC 8th edition and had ≥ 3 prior surgeries for CSCC. Similar proportions of patients had R0 resection or were not evaluable across treatment arms (R0, R1 was a post hoc analysis). A comparison of the cemiplimab and placebo groups reveals a slightly higher proportion of patients with microscopic residual disease in the cemiplimab group (3% difference). It is worth noting that these findings only pertain to half of the study population as this information was not required upon enrollment into the pivotal study. Radiotherapy was employed in all patients with the majority of patients treated with IMRT (75%) and total dose of 60-69 Gy (76%). Patients must have received a minimum Biologically Equivalent Dose (BED) to the site of previous gross disease of 50 Gy. This approach aligns with the current standard of care in radiotherapy for this particular disease setting. The median time from end of RT to randomization was 1.3 months (~5.6 weeks). A short time after RT can pose difficulties in efficacy and safety assessments. This is because RT-related tissue changes, such as tumour oedema, other artifacts, and RT toxicity, require longer time to resolve and therefore might lead to challenges in interpreting images and assessing the effects of the primary treatment introducing some uncertainties to the efficacy of the new treatment (cemiplimab).

Efficacy data and additional analyses

At the data cut-off on 04 Oct 2024, when the first planned interim analysis was conducted, a total of 89 DFS events had been observed, with a median follow-up of 18.3 months (cemiplimab:23.5 months; placebo:13.2 months). As per Investigator evaluation of images, cemiplimab was superior to placebo to prevent recurrence or death in patients at high-risk of recurrence after surgery and RT for CSCC. With 11.5% of DFS events in the cemiplimab arm and 31.6% in the placebo arm, the HR for DFS was 0.319 (95% CI 0.199, 0.511; <0.0001), noting that mDFS was NR in the cemiplimab arm vs. 49.4 months in the placebo arm. The p-value crossed the pre-specified efficacy threshold of 0.0032 for statistical significance in favour of the cemiplimab arm, turning the first interim analysis for DFS into the primary analysis. The K-M curves separate as of the third month from randomisation and remain separated.

Additional sensitivity analysis was performed where SPT (second primary tumour) was counted as event. The results of this analysis are statistically significant with HR 0.425 (95%CI: 0.299, 0.603; $p<0.0001$), which is reassuring. The results of sensitivity analysis where patients who started new anticancer therapy were censored (not EMA preferred approach) yield similar results to the primary analysis. More patients in the cemiplimab arm than in the placebo arm were censored. Most patients were censored due to "last imaging without recurrence" and that patients censored due to missing post baseline assessments (treated or not treated) were few and evenly distributed in both treatment arms. There were no patients with non-evaluable disease.

While the control of type I error at IA1 is methodologically acceptable, concerns remain regarding the maturity of the data and the robustness of the conclusions, particularly given that they are based on the endpoint of DFS, which was Investigator assessed. Although the Kaplan-Meier curves suggest that most DFS events occur within the first 12 months and a plateau may be emerging thereafter. The MAH submitted data with an additional 6 months follow-up (new DCO 07 Apr 2025). During the additional follow-up time few events occurred ($n=8$: 5 in cemiplimab and 3 in placebo arm) leading to slight change in HR (updated HR 0.354 vs. HR 0.319 previously). Results are still statistically significant with p-value <0.0001 and relatively wide 95% CI (updated 95%CI: 0.229, 0.548). Of note, the median DFS is not reached in both arms with this update. The maturity of DFS is 23% with 29 (13.9%) and 68 (33%) events in the cemiplimab and placebo arm respectively. Overall, the updated results provide some reassurance that the DFS benefit observed in the primary analysis is maintained with longer follow-up, despite the fact that the expected plateau of KM curves is not reached yet.

It is agreed that the majority of DFS events most likely occurred already, however the risk of recurrence for CSCC is highest within the first three years from the diagnosis. Updated results of DFS are expected to further inform on the long-term benefit and the persistence of treatment effect after discontinuation of adjuvant cemiplimab, especially given the low number of events and duration of follow-up at timepoint of primary analysis. The updated descriptive DFS and final OS data will be provided as a post-approval recommendation **(REC)**. The study gives rise to further clinical considerations. 1) Recurrence or development of a new tumor that cannot be managed with surgery and/or radiotherapy after adjuvant treatment with cemiplimab presents a significant challenge as there are only limited treatment options left in this setting. 2) Since a sizeable number of patients with CSCC can be cured by surgery and radiotherapy alone there is a risk of potential overtreatment by adding cemiplimab in the adjuvant setting. However, the magnitude of improvement in DFS is considered to 1) justify that cemiplimab in the adjuvant setting should be an option and also 2) to outweigh the risk of potential overtreatment and associated adverse events.

All secondary endpoints were Investigator assessed and included FFLR (Freedom from locoregional recurrence), FFDR (Freedom from distant recurrence), SPT and OS. A trend toward reduced number of both locoregional and distant recurrences is noticed for the cemiplimab arm but low number of events per arm prevents from drawing any meaningful conclusions. The updated results of all secondary endpoints with additional 6 months FU (DCO 07 Apr 2025) are overall consistent with the primary analysis due to low number of events (n=4 for FFLRR, n=4 for FFDR, n=11 for SPT and n=8 for OS). OS data are highly immature with only 15 (7.2% events) and 18 (8.7%) deaths observed in the cemiplimab and placebo arm, respectively but final OS data will be provided post approval (REC). The trial design of Study 1788 does not allow for a conclusion on if adjuvant cemiplimab treatment in comparison with treating recurrent disease with cemiplimab leads to an increase in overall survival. In other words, if moving treatment with cemiplimab from the recurrent setting to the adjuvant setting will result in improved survival.

The results of DFS analysis in the prespecified subgroups align with the primary analysis observed in the ITT population. Consistent with the primary analysis, the results from the subgroup analyses are maintained with an additional six months of follow-up. However, the small sample sizes of some subgroups and the overall low number of events in both arms introduce uncertainty regarding the observed results.

PD-L1 analysis was an exploratory analysis in the study 1788. Of 415 patients in the ITT population, PD-L1 status was known for 394 patients (~95%). A validated assay for NSCLC (SP263) was used to assess the PD-L1 positivity on tumor cells (TPS). This assay is not clinically validated in CSCC but has a high concordance rate in NSCLC. Testing with any other assay (22C3 used in study 1540) is not possible due to the expiration of slide stability for the 22C3 assay. The DFS benefit of adjuvant treatment with cemiplimab was observed regardless of PD-L1 status in the prespecified threshold. This result can be also influenced by the immature data.

PRO data was collected using the EORTC QLQ-C30 and the EQ-5D-3L questionnaires. No clinically meaningful differences in the mean scores were observed between treatment arms.

2.4.4. Conclusions on the clinical efficacy

The results of pivotal study 1788 show statically significant improvement in DFS with adjuvant cemiplimab over placebo for patients at a high-risk of recurrence after surgery and radiotherapy for CSCC. Updated results of DFS and OS are expected to further inform on the long-term benefit and the

persistence of treatment effect after discontinuation of adjuvant cemiplimab, and will be provided post-approval (REC).

2.5. Clinical safety

Introduction

In the EU, cemiplimab holds indications in metastatic cutaneous squamous cell carcinoma (mCSCC), metastatic basal cell carcinoma (BCC), metastatic cervical cancer and metastatic non-small cell lung cancer (mNSCLC). The existing safety profile in the metastatic setting is based on multiple and large randomized studies such as R2810-ONC-1624 in mNSCLC (n = 710), R2810-ONC-1676 in metastatic cervical cancer (n = 608) as well as the non-randomized R2810-ONC-1540 in mCSCC (n = 358).

This application concerns an extension of indication to include adjuvant treatment for CSCC and includes data from the pivotal phase 3 study R2810-ONC-1788. It is the first-time safety data had been collected on cemiplimab in an adjuvant setting.

Table 44: List of studied in the monotherapy pool (N=1281)

Studies/Patients	Data Cutoff
Study 1540 (CSCC) (N = 358)	
Patients in Group 1, Group 2, and Group 3	Final data
Patients in Group 6 primary analysis	25 Oct 2021
Study 1620 (BCC):	20 May 2021
All patients (N = 138)	
Study 1423 (FIH):	Final data
All patients who received cemiplimab monotherapy (N = 130)	
Study 1624 (NSCLC)[a]	01 Mar 2020
Cemiplimab monotherapy (N = 355)	
Study 1676 (cervical):	04 Jan 2021
All patients who received cemiplimab monotherapy (N = 300)	

[a] excluding crossover data

Abbreviations: BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; FIH, first-in-human; NSCLC, non-small cell lung cancer.

Patient exposure

Table 45: Duration of Study Follow-up from Randomization to Cutoff Date (FAS)

	Cemiplimab (N = 209)	Placebo (N = 206)	Total (N = 415)
Duration of Study Follow-up (months)			
n	209	206	415
Mean (SD)	25.7 (15.36)	25.7 (16.06)	25.7 (15.69)
Median	24.5	23.8	24.0
Q1: Q3	12.3 : 36.7	12.1 : 36.9	12.1 : 36.7
Min : Max	2 : 61	2 : 64	2 : 64
Duration of Study Follow-Up, n (%)			
≥6 months	185 (88.5%)	183 (88.8%)	368 (88.7%)
≥12 months	157 (75.1%)	155 (75.2%)	312 (75.2%)
≥24 months	109 (52.2%)	102 (49.5%)	211 (50.8%)
≥36 months	54 (25.8%)	54 (26.2%)	108 (26.0%)
≥48 months	24 (11.5%)	28 (13.6%)	52 (12.5%)

Abbreviations: Max, Maximum; Min, Minimum; Q, Quartile; SD, Standard deviation

Note: Duration of study follow up from randomization to DCO includes patients in Part 1 and Part 2, regardless of patient discontinuation.

Table 46: Treatment Exposure - (Safety Analysis Set) – Part 1

	Cemiplimab (N = 205)	Placebo (N = 204)
Number of patients who received 350 mg Q3W only, n (%)	65 (31.7%)	64 (31.4%)
Number of patients who received 350 mg Q3W followed by 700 mg Q6W, n (%)	140 (68.3%)	140 (68.6%)
Duration of Treatment Exposure (weeks) [1]		
N	205	204
Mean (SD)	37.5 (15.67)	36.1 (15.13)
Median	47.9	47.7
Q1 : Q3	25.7 : 48.0	24.0 : 48.0
Min:Max	3 : 52	3 : 51
Duration of treatment Exposure, n (%)		
≥3 weeks	205 (100%)	204 (100%)
≥6 weeks	196 (95.6%)	201 (98.5%)
≥12 weeks	181 (88.3%)	182 (89.2%)
≥18 weeks	168 (82.0%)	170 (83.3%)
≥24 weeks	158 (77.1%)	154 (75.5%)
≥36 weeks	143 (69.8%)	127 (62.3%)
≥48 weeks	102 (49.8%)	86 (42.2%)
Number of administrations of study treatment		
N	205	204
Mean (SD)	9.0 (3.80)	8.9 (3.74)
Median	10.0	9.0
Q1 : Q3	7.0 : 10.0	6.0 : 10.0
Min: Max	1 : 16	1 : 16
Number of administrations of study treatment, n (%)		
≥4	181 (88.3%)	185 (90.7%)
≥6	166 (81.0%)	161 (78.9%)
≥8	150 (73.2%)	134 (65.7%)
≥10	113 (55.1%)	101 (49.5%)
≥12	33 (16.1%)	33 (16.2%)
≥14	26 (12.7%)	28 (13.7%)

[1] Duration of treatment exposure (weeks) is defined as [minimum (date of last dose + 21 days, DCO date+1, date of death+1, date of first dose of Part 2 cemiplimab) - date of first dose]/7 for participants who received 350 mg Q3W only and [minimum (date of last dose + 42 days, DCO date+1, date of death+1, date of first dose of Part 2 cemiplimab) - date of first dose]/7 for participants who received 350 mg Q3W followed by 700 mg Q6W.

Abbreviations: DCO, Data cutoff; Max, Maximum; Min, Minimum; Q, Quartile; Q3W, Every 3 weeks; Q6W, Every 6 weeks; SD, Standard deviation

Adverse events

Table 47: Participant Disposition (FAS) – Part 1 and End of Study

	Cemiplimab (N = 209)	Placebo (N = 206)
Participants randomized but not treated, n (%)	4 (1.9%)	2 (1.0%)
Participants who completed treatment, n (%)	125 (59.8%)	110 (53.4%)
Participants who are ongoing treatment, n (%)	36 (17.2%)	33 (16.0%)
Participants who did not complete treatment, n (%)	44 (21.1%)	61 (29.6%)
Reason for treatment discontinuation, n (%)		
Disease relapse	10 (4.8%)	50 (24.3%)
Adverse event	19 (9.1%)	3 (1.5%)
Withdrawal by subject	8 (3.8%)	5 (2.4%)
Physician decision	4 (1.9%)	2 (1.0%)
Other [1]	2 (1.0%)	0
Death	0	1 (0.5%)
Withdrawal of consent	1 (0.5%)	0
Participants who completed the study, n (%)	0	0
Participants who are ongoing in the study, n (%)	187 (89.5%)	175 (85.0%)
Participants who did not complete the study, n (%)	22 (10.5%)	31 (15.0%)
Reason for not completing the study, n (%)		
Death	12 (5.7%)	13 (6.3%)
Withdrawal of consent	2 (1.0%)	9 (4.4%)
Physician decision	2 (1.0%)	2 (1.0%)
Sponsor request	1 (0.5%)	2 (1.0%)
Disease relapse	2 (1.0%)	0
Lost to follow-up	0	2 (1.0%)
Withdrawal by subject	2 (1.0%)	1 (0.5%)
Other [1]	1 (0.5%)	2 (1.0%)

[1] Details are provided in Module 5.3.5.1 Study 1788 CSR PTLs 16.2.1.1.1 and 16.2.1.1.3.

Abbreviations: EOS, End of study

Table 48: Overview of Treatment-Emergent Adverse Events (SAS) – Part 1

Participant with at least one	Cemiplimab (N = 205)	Placebo (N = 204)
TEAE	187 (91.2%)	182 (89.2%)
TEAE with any NCI grade 3/4/5	49 (23.9%)	29 (14.2%)
TE-SAE	36 (17.6%)	19 (9.3%)
TEAE leading to study treatment discontinuation	20 (9.8%)	3 (1.5%)
TEAE leading to death	2 (1.0%)	2 (1.0%)
TEAE leading to study treatment interruption/delay	46 (22.4%)	26 (12.7%)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; SAE – Serious adverse event; TE, Treatment-emergent; TEAE, Treatment-emergent adverse event;

Note: NCI grades were coded using CTCAE Version 5.

Table 49: Treatment-Emergent Adverse Events by Preferred Term and NCI Grade with All Grades in >5% of Patients in Any Treatment Arm or Grade 3/4/5 in >2% of Patients in Any Treatment Arm (SAS) – Part 1

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N = 205)		Placebo (N = 204)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of participants with at least one such TEAE	187 (91.2%)	49 (23.9%)	182 (89.2%)	29 (14.2%)
Skin and subcutaneous tissue disorders	111 (54.1%)	6 (2.9%)	85 (41.7%)	1 (0.5%)
Pruritus	33 (16.1%)	1 (0.5%)	25 (12.3%)	0
Rash	33 (16.1%)	1 (0.5%)	18 (8.8%)	0
Rash maculo-papular	23 (11.2%)	0	12 (5.9%)	0
Actinic keratosis	20 (9.8%)	0	16 (7.8%)	1 (0.5%)
Infections and infestations	87 (42.4%)	10 (4.9%)	78 (38.2%)	11 (5.4%)
COVID-19	15 (7.3%)	0	18 (8.8%)	0
Skin infection	6 (2.9%)	0	11 (5.4%)	2 (1.0%)
General disorders and administration site conditions	75 (36.6%)	2 (1.0%)	73 (35.8%)	0
Fatigue	45 (22.0%)	1 (0.5%)	44 (21.6%)	0
Oedema peripheral	11 (5.4%)	0	5 (2.5%)	0
Gastrointestinal disorders	73 (35.6%)	5 (2.4%)	72 (35.3%)	1 (0.5%)
Diarrhoea	32 (15.6%)	3 (1.5%)	38 (18.6%)	0
Nausea	15 (7.3%)	0	13 (6.4%)	0
Constipation	12 (5.9%)	0	17 (8.3%)	0
Dry mouth	11 (5.4%)	0	8 (3.9%)	0
Musculoskeletal and connective tissue disorders	61 (29.8%)	3 (1.5%)	53 (26.0%)	0
Arthralgia	26 (12.7%)	0	25 (12.3%)	0
Back pain	11 (5.4%)	0	8 (3.9%)	0
Nervous system disorders	46 (22.4%)	2 (1.0%)	45 (22.1%)	3 (1.5%)
Headache	14 (6.8%)	0	18 (8.8%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44 (21.5%)	2 (1.0%)	51 (25.0%)	8 (3.9%)
Bowen's disease[a]	16 (7.8%)	1 (0.5%)	21 (10.3%)	2 (1.0%)
Squamous cell carcinoma of skin[b]	16 (7.8%)	1 (0.5%)	20 (9.8%)	4 (2.0%)
Basal cell carcinoma	14 (6.8%)	1 (0.5%)	16 (7.8%)	2 (1.0%)

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N = 205)		Placebo (N = 204)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Investigations	39 (19.0%)	6 (2.9%)	23 (11.3%)	0
Alanine aminotransferase increased	12 (5.9%)	4 (2.0%)	3 (1.5%)	0
Endocrine disorders	33 (16.1%)	3 (1.5%)	7 (3.4%)	0
Hypothyroidism	24 (11.7%)	1 (0.5%)	6 (2.9%)	0
Hyperthyroidism	12 (5.9%)	0	1 (0.5%)	0
Respiratory, thoracic and mediastinal disorders	29 (14.1%)	0	26 (12.7%)	2 (1.0%)
Cough	12 (5.9%)	0	7 (3.4%)	0
Vascular disorders	20 (9.8%)	6 (2.9%)	19 (9.3%)	4 (2.0%)
Hypertension	8 (3.9%)	5 (2.4%)	11 (5.4%)	4 (2.0%)
Psychiatric disorders	17 (8.3%)	1 (0.5%)	14 (6.9%)	1 (0.5%)
Insomnia	11 (5.4%)	0	5 (2.5%)	0

[a] Bowen's disease' refers to SCCs that were confirmed in-situ histologically. These are not disease recurrences per protocol definition and are not SPTs per protocol definition.

[b] SCC of skin' consisted of new SPTs that were confirmed invasive histologically or SCCs with unreported histology. Study sites were not required to report SPTs on the AE page in the EDC, because there is a separate page in the EDC for reporting SPTs. The summary of SPTs in the efficacy section is the official output for SPTs, not this AE table.

Abbreviations: AE, adverse event; COVID-19, Coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; EDC, Electronic data capture (database); MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, Preferred term; SCC, Squamous cell carcinoma; SOC, System organ class; SPT, Second primary cutaneous squamous cell carcinoma tumor; TEAE, Treatment-emergent adverse event

Note: All AEs were coded using MedDRA Version 27.0. NCI grades were coded using CTCAE Version 5.

Note: A patient is counted only once per the worst grade for multiple occurrences within a SOC/PT.

Note: For SOC, the table is sorted by decreasing frequency in the cemiplimab arm. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab arm.

Table 50: Comparison of Adverse Events Between Study 1788 (Part 1) and Monotherapy Pool (All Grades and Grade ≥3)

System Organ Class Preferred Term	Cemiplimab (N = 205)		Placebo (N = 204)		Monotherapy Pool (N = 1281)	
	All Grades %	Grades 3/4/5 %	All Grades %	Grades 3/4/5 %	All Grades %	Grades 3/4/5 %
Infections and infestations						
Upper respiratory tract infection [a]	11.2	0	8.8	0	10.9	0.4
Urinary tract infection [b]	4.4	1.0	2.5	0	8.4	2.3
Blood and lymphatic system disorders						
Anaemia	2.0	0.5	2.9	0.5	15.0	5.2
Immune system disorders						
Infusion related reaction	1.0	0	2.0	0	3.3	<0.1
Thrombocytopenia [c]	1.0	0.5	0	0	0.9	0
Sjogren's syndrome	0	0	0	0	0.2	0
Endocrine disorders						
Hypothyroidism [d]	10.7	0.5	2.5	0	6.8	<0.1
Hyperthyroidism	5.4	0	0	0	3.0	<0.1
Thyroiditis [e]	0	0	0	0	0.6	0
Adrenal insufficiency	1.5	1.0	0	0	0.5	0.5
Hypophysitis [f]	0	0	0	0	0.5	0.2
Type 1 diabetes mellitus [g]	0	0	0	0	<0.1	<0.1

System Organ Class Preferred Term	Cemiplimab (N = 205)		Placebo (N = 204)		Monotherapy Pool (N = 1281)	
	All Grades %	Grades 3/4/5 %	All Grades %	Grades 3/4/5 %	All Grades %	Grades 3/4/5 %
Nervous system disorders						
Headache	6.8	0	8.8	0	8.0	0.3
Peripheral neuropathy [h]	1.0	0	0	0	1.3	<0.1
Meningitis [i]	0	0	0	0	<0.1	<0.1
Encephalitis	0	0	0	0	<0.1	<0.1
Myasthenia gravis	0	0	0	0	<0.1	0
Paraneoplastic encephalomyelitis	0	0	0	0	<0.1	<0.1
Chronic inflammatory demyelinating polyradiculoneuropathy	0	0	0	0	<0.1	0
Eye disorders						
Keratitis	0	0	0	0	<0.1	0
Uveitis	0	0	0	0	<0.1	<0.1
Cardiac disorders						
Myocarditis [j]	0.5	0.5	0	0	0.5	0.3
Pericarditis [k]	0	0	0	0	0.3	0.2
Vascular disorders						
Hypertension [l]	3.9	2.4	5.4	2.0	5.7	2.6
Metabolism and nutrition disorders						
Decreased appetite	3.4	0	2.5	0	13.0	0.6
Respiratory, thoracic and mediastinal disorders						
Cough [m]	6.8	0	4.4	0	10.8	0.2
Dyspnoea [n]	3.4	0	2.0	0	9.7	1.2
Pneumonitis [o]	2.0	0	1.0	0	3.3	1.1
Gastrointestinal disorders						
Diarrhoea	15.6	1.5	18.6	0	16.3	0.7
Nausea	7.3	0	6.4	0	14.7	0.2
Constipation	5.9	0	8.3	0	12.3	0.2
Abdominal pain [p]	2.9	0	3.4	0	11.5	0.7

System Organ Class Preferred Term	Cemiplimab (N = 205)		Placebo (N = 204)		Monotherapy Pool (N = 1281)	
	All Grades %	Grades 3/4/5 %	All Grades %	Grades 3/4/5 %	All Grades %	Grades 3/4/5 %
Vomiting	3.4	0	2.9	0	9.9	0.2
Colitis [q]	1.5	1.0	1.0	0.5	2.0	0.8
Stomatitis	0.5	0	0	0	1.8	<0.1
Gastritis [r]	0	0	0	0	0.2	0
Hepatobiliary disorders						
Hepatitis [s]	2.0	1.5	0.5	0	2.7	1.8
Skin and subcutaneous skin disorders						
Rash [t]	36.6	2.0	21.1	0	21.4	1.6
Pruritus [u]	16.1	0.5	12.3	0	12.7	0.2
Actinic keratosis	9.8	0	7.8	0.5	3.7	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain [v]	23.9	0.5	23.5	0	28.3	1.8
Arthritis [w]	0.5	0	0.5	0	0.9	0.2
Myositis [x]	0.5	0.5	0	0	0.3	<0.1
Muscular weakness	0	0	0	0	0.2	0
Polymyalgia rheumatica	0	0	0	0	0.2	0
Renal and urinary disorders						
Nephritis [y]	0.5	0.5	0	0	1.2	0.2
General disorders and administration site conditions						
Fatigue [z]	26.8	1.0	26.5	0	29.9	2.6
Pyrexia [aa]	1.5	0	1.5	0	8.7	0.2
Oedema [bb]	9.3	0	5.9	0	7.9	0.4
Investigations						
Alanine aminotransferase	5.4	2.0	1.5	0	4.6	0.5
Aspartate aminotransferase	4.9	0.5	0.5	0	4.4	0.7
Blood alkaline phosphatase increased	1.5	0.5	0	0	1.9	0.2
Blood creatinine increased	1.0	0	0.5	0	1.6	0

System Organ Class Preferred Term	Cemiplimab (N = 205)		Placebo (N = 204)		Monotherapy Pool (N = 1281)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
	%	%	%	%	%	%
Blood thyroid stimulating hormone increased	1.5	0	1.0	0	0.8	0
Transaminases increased	0	0	0	0	0.4	<0.1
Blood bilirubin increased	0.5	0	0	0	0.4	<0.1
Blood thyroid stimulating hormone decreased	0	0	1.0	0	<0.1	0

[a] Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, respiratory tract infection, rhinitis, viral upper respiratory tract infection, viral respiratory tract infection, pharyngitis, laryngitis, viral rhinitis, acute sinusitis, tonsillitis, tracheitis, influenza like illness, and influenza.

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

[c] Thrombocytopenia includes thrombocytopenia and immune thrombocytopenia.

[d] Hypothyroidism includes hypothyroidism and immune-mediated hypothyroidism.

[e] Thyroiditis includes thyroiditis, autoimmune thyroiditis, and immune-mediated thyroiditis.

[f] Hypophysitis includes hypophysitis and lymphocytic hypophysitis.

[g] Type 1 diabetes mellitus includes diabetic ketoacidosis and Type 1 diabetes mellitus.

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

[i] Meningitis includes aseptic meningitis.

[j] Myocarditis includes myocarditis, autoimmune myocarditis, and immune-mediated myocarditis.

[k] Pericarditis includes autoimmune pericarditis and pericarditis.

[l] Hypertension includes hypertension and hypertensive crisis.

[m] Cough includes cough, productive cough, and upper-airway cough syndrome.

[n] Dyspnea includes dyspnea and dyspnea exertional.

[o] Pneumonitis includes pneumonitis, immune-mediated lung disease, interstitial lung disease, and pulmonary fibrosis.

[p] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal distension, abdominal pain lower, abdominal discomfort, and gastrointestinal pain.

[q] Colitis includes colitis, autoimmune colitis, enterocolitis, and immune-mediated enterocolitis.

[r] Gastritis includes gastritis and immune-mediated gastritis.

[s] Hepatitis includes autoimmune hepatitis, immune-mediated hepatitis, hepatitis, hepatotoxicity, hyperbilirubinemia, hepatocellular injury, hepatic failure, abnormal hepatic function, and hepatic cytolysis.

[t] Rash includes rash, rash maculo-papular, dermatitis, erythema, rash pruritic, urticaria, rash erythematous, dermatitis bullous, dermatitis acneiform, rash macular, psoriasis, rash papular, dyshidrotic eczema, pemphigoid, autoimmune dermatitis, dermatitis allergic, atopic dermatitis, drug eruption, erythema nodosum, skin reaction, skin toxicity, dermatitis exfoliative, dermatitis exfoliative generalised, dermatitis psoriasiform, erythema multiforme, exfoliative rash, immune-mediated dermatitis, lichen planus, parapsoriasis, eczema, dermatitis contact, eczema nummular, hand dermatitis, pustular psoriasis, rosacea, acne, eczema asteatotic, rash pustular, and rash vesicular.

[u] Pruritus includes pruritus and allergic pruritus.

[v] Musculoskeletal pain includes arthralgia, back pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal pain, spinal pain, musculoskeletal stiffness, musculoskeletal discomfort, non-cardiac chest pain, and pain in jaw.

[w] Arthritis includes arthritis, polyarthritis, autoimmune arthritis, and immune-mediated arthritis.

[x] Myositis includes myositis and dermatomyositis.

[y] Nephritis includes acute kidney injury, renal impairment, immune-mediated nephritis, nephritis, renal failure, tubulointerstitial nephritis, and nephropathy toxic.

[z] Fatigue includes fatigue, asthenia, malaise, and lethargy.

[aa] Pyrexia includes pyrexia, hyperthermia, and hyperpyrexia.

[bb] Edema includes peripheral edema, face edema, peripheral swelling, face swelling, localised edema, generalised edema, and swelling.

Table 51: Treatment-Emergent Serious Adverse Events (in $\geq 1\%$ in Any Arm) by System Organ Class and Preferred Term (SAS) – Part 1

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N = 205)	Placebo (N = 204)
Number of participants with at least one such TEAE	36 (17.6%)	19 (9.3%)
Infections and infestations	10 (4.9%)	9 (4.4%)
Pneumonia	2 (1.0%)	2 (1.0%)
Cellulitis	1 (0.5%)	2 (1.0%)
Skin infection	0	2 (1.0%)
Endocrine disorders	3 (1.5%)	0
Adrenal insufficiency	2 (1.0%)	0
Gastrointestinal disorders	3 (1.5%)	1 (0.5%)
Diarrhoea	2 (1.0%)	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, Preferred Term; SOC, System Organ Class; TEAE, Treatment-Emergent adverse event

Note: All adverse events were coded using MedDRA Version 27.0. NCI grades were coded using CTCAE Version 5

Note: A patient is counted only once per the worst grade for multiple occurrences within a SOC/PT.

Note: For SOC, the table is sorted by decreasing frequency in the cemiplimab arm. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab arm.

Adverse drug reactions

The MAH has updated section 4.8 of the SmPC to include the population adult patients with Cutaneous Squamous Cell Carcinoma at high risk of recurrence after surgery and radiation (study R2810-ONC-1788). The safety of cemiplimab as monotherapy in the adjuvant treatment of patients with CSCC at high risk of recurrence was evaluated in 205 patients in the C-POST study.

Adverse drug reactions were defined as AEs that met at least one of the following criteria:

- TEAEs that occurred in at least 10% of patients in cemiplimab arm and at least 3% higher than the rate in the placebo arm
- Identified imAEs that occurred in at least 1 patient
- IRRs that occurred in at least 1 patient (using the PT of Infusion-related reaction)

The adverse drug reactions (ADRs) observed in patients with high-risk CSCC treated with adjuvant cemiplimab compared to placebo in Study 1788 based on the first criteria above are listed below.

Table 52: Tabulated List of Adverse Reactions in $\geq 10\%$ of Patients with High-Risk CSCC Treated with Adjuvant Cemiplimab in Study 1788 (All, Grade ≥ 3)

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N = 205)		Placebo (N = 204)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Endocrine disorders				
Hypothyroidism	24 (11.7%)	1 (0.5%)	6 (2.9%)	0
Skin and subcutaneous tissue disorders				
Rash [a]	75 (36.6%)	4 (2.0%)	43 (21.1%)	0
Pruritus	33 (16.1%)	1 (0.5%)	25 (12.3%)	0

[a] Rash includes Rash, Rash maculo-papular, Rash macular, Dermatitis, Eczema, Rash erythematous, Rash pruritic, Dermatitis acneiform, Psoriasis, Rash papular, Dermatitis contact, Drug eruption, Eczema nummular, Erythema, Exfoliative rash, Hand dermatitis, Immune-mediated dermatitis, Lichen planus, Pemphigoid, Pustular psoriasis, Rosacea, Urticaria, Acne, Eczema asteatotic, Rash pustular, Rash vesicular.

Source: Module 5.3.5.1 Study 1788 CSR PTT 14.3.1.2.11

Table 53: Tabulated List of imAE Adverse Reactions in Patients with High-Risk CSCC Treated with Adjuvant Cemiplimab in Study 1788 (All, Grade ≥ 3)

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N = 205)		Placebo (N = 204)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Endocrine disorders				
Hypothyroidism	22 (10.7%)	1 (0.5%)	5 (2.5%)	0
Hyperthyroidism	11 (5.4%)	0	0	0
Adrenal insufficiency	3 (1.5%)	2 (1.0%)	0	0
Nervous system disorders				
Peripheral neuropathy [a]	2 (1.0%)	0	0	0
Cardiac disorders				
Myocarditis	1 (0.5%)	1 (0.5%)	0	0
Respiratory, thoracic and mediastinal disorders				
Pneumonitis [b]	4 (2.0%)	0	2 (1.0%)	0

Gastrointestinal disorders				
Diarrhoea [c]	24 (11.7%)	4 (2.0%)	19 (9.3%)	1 (0.5%)
Hepatobiliary disorders				
Hepatitis [d]	4 (2.0%)	3 (1.5%)	1 (0.5%)	0
Skin and subcutaneous skin disorders				
Rash [e]	63 (30.7%)	3 (1.5%)	25 (12.3%)	0
Pruritus	29 (14.1%)	1 (0.5%)	19 (9.3%)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [f]	13 (6.3%)	0	14 (6.9%)	0
Myositis	1 (0.5%)	1 (0.5%)	0	0
Investigations				
Liver function test abnormalities [g]	14 (6.8%)	5 (2.4%)	4 (2.0%)	0
Blood thyroid stimulating hormone increased	3 (1.5%)	0	2 (1.0%)	0

[a] Peripheral neuropathy includes Paraesthesia and Peripheral sensory neuropathy.

[b] Pneumonitis includes Pneumonitis and Immune-mediated lung disease.

[c] Diarrhoea includes Diarrhoea, Colitis, Immune-mediated enterocolitis, and Enterocolitis.

[d] Hepatitis includes Immune-mediated hepatitis, Hepatitis, Hepatotoxicity, and Hepatic cytolysis.

[e] Rash includes Rash, Rash maculo-papular, Rash macular, Dermatitis, Rash erythematous, Rash papular, Dermatitis acneiform, Dermatitis contact, Eczema, Eczema nummular, Immune-mediated dermatitis, Lichen planus, Pemphigoid, Psoriasis, Pustular psoriasis, Rash pruritic, Acne, and Erythema.

[f] Musculoskeletal pain includes Arthralgia, Bone pain, Musculoskeletal discomfort, Myalgia, Pain in extremity, Back pain, Neck pain, and Pain in jaw.

[g] Liver function test abnormalities include Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Blood bilirubin increased, and Hypertransaminasaemia.

Serious adverse event/deaths/other significant events

Table 54: Treatment-Emergent Serious Adverse Events (in $\geq 1\%$ in Any Arm) by System Organ Class and Preferred Term (SAS) – Part 1

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N = 205)	Placebo (N = 204)
Number of participants with at least one such TEAE	36 (17.6%)	19 (9.3%)
Infections and infestations	10 (4.9%)	9 (4.4%)
Pneumonia	2 (1.0%)	2 (1.0%)
Cellulitis	1 (0.5%)	2 (1.0%)
Skin infection	0	2 (1.0%)
Endocrine disorders	3 (1.5%)	0
Adrenal insufficiency	2 (1.0%)	0
Gastrointestinal disorders	3 (1.5%)	1 (0.5%)
Diarrhoea	2 (1.0%)	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, Preferred Term; SOC, System Organ Class; TEAE, Treatment-Emergent adverse event

Note: All adverse events were coded using MedDRA Version 27.0. NCI grades were coded using CTCAE Version 5

Note: A patient is counted only once per the worst grade for multiple occurrences within a SOC/PT.

Note: For SOC, the table is sorted by decreasing frequency in the cemiplimab arm. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab arm.

Table 55: Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term (SAS) – Part 1

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N = 205)	Placebo (N = 204)
Number of participants with at least one such TEAE	2 (1.0%)	2 (1.0%)
Infections and infestations	1 (0.5%)	1 (0.5%)
Pneumonia	1 (0.5%)	1 (0.5%)
Musculoskeletal and connective tissue disorders	1 (0.5%)	0
Myositis	1 (0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5%)
Lung neoplasm malignant	0	1 (0.5%)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, Preferred Term; SOC, System Organ Class; TEAE, Treatment-emergent adverse event

Note: All adverse events were coded using MedDRA Version 27.0.

Note: A patient is counted only once per the worst grade for multiple occurrences within a SOC/PT.

Note: For SOCs, the table is sorted by decreasing frequency in the cemiplimab arm. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab arm.

Laboratory findings

Table 56: Hematology: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade (Safety Analysis Set) - Part 1

Parameter (CTCAE Term)	<u>Cemiplimab</u> (N = 205)		Placebo (N = 204)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of patients with at least one lab abnormality, n (%)	124/203 (61.1%)	14/203 (6.9%)	104/203 (51.2%)	8/203 (3.9%)
Hemoglobin (Anemia)	47/203 (23.2%)	1/203 (0.5%)	32/203 (15.8%)	1/203 (0.5%)
Hemoglobin (Hemoglobin increased)	2/203 (1.0%)	0/203	2/203 (1.0%)	0/203
Leukocytes (White blood cell decreased)	33/203 (16.3%)	0/203	31/203 (15.3%)	0/203
Lymphocytes (Lymphocyte count decreased)	65/203 (32.0%)	13/203 (6.4%)	55/203 (27.1%)	6/203 (3.0%)
Lymphocytes (Lymphocyte count increased)	3/203 (1.5%)	0/203	2/203 (1.0%)	0/203
Neutrophils (Neutrophil count decreased)	13/203 (6.4%)	0/203	12/202 (5.9%)	1/202 (0.5%)
Platelets (Platelet count decreased)	18/203 (8.9%)	1/203 (0.5%)	23/203 (11.3%)	0/203

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute

Note: NCI grades were coded using CTCAE Version 5.

Note: Percentages are based on the number of patients with at least one post-baseline value available for that parameter.

Note: Post-baseline value is for on-treatment period only.

Note: A patient is counted only once for multiple occurrences for the same parameter.

Source: Module 5.3.5.1 Study 1788 CSR PTT 14.3.3.1.1

Table 57: Electrolytes: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade (Safety Analysis Set) - Part 1

Parameter (CTCAE Term)	<u>Cemiplimab</u> (N = 205)		Placebo (N = 204)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of patients with at least one lab abnormality, n (%)	81/203 (39.9%)	6/203 (3.0%)	93/203 (45.8%)	4/203 (2.0%)
Calcium (Hypercalcemia (Uncorrected Calcium))	14/202 (6.9%)	1/202 (0.5%)	11/202 (5.4%)	0/202
Calcium (Hypocalcemia (Uncorrected Calcium))	15/202 (7.4%)	2/202 (1.0%)	16/202 (7.9%)	2/202 (1.0%)
Potassium (Hyperkalemia)	29/203 (14.3%)	1/203 (0.5%)	35/203 (17.2%)	0/203
Potassium (Hypokalemia)	11/203 (5.4%)	2/203 (1.0%)	10/203 (4.9%)	1/203 (0.5%)
Sodium (Hypernatremia)	6/203 (3.0%)	0/203	4/203 (2.0%)	0/203
Sodium (Hyponatremia)	37/203 (18.2%)	1/203 (0.5%)	37/203 (18.2%)	1/203 (0.5%)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute

Note: NCI grades were coded using CTCAE Version 5.

Note: Percentages are based on the number of patients with at least one post-baseline value available for that parameter.

Note: Post-baseline value is for on-treatment period only.

Note: A patient is counted only once for multiple occurrences for the same parameter.

Table 58: Liver Parameters: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade (Safety Analysis Set) - Part 1

Parameter (CTCAE Term)	<u>Cemiplimab</u> (N = 205)		Placebo (N = 204)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of patients with at least one lab abnormality, n (%)	119/203 (58.6%)	10/203 (4.9%)	84/203 (41.4%)	1/203 (0.5%)
Alanine Aminotransferase (Alanine aminotransferase increased)	49/203 (24.1%)	8/203 (3.9%)	24/203 (11.8%)	0/203
Albumin (Hypoalbuminemia)	44/203 (21.7%)	2/203 (1.0%)	24/203 (11.8%)	0/203
Alkaline Phosphatase (Alkaline phosphatase increased)	31/203 (15.3%)	3/203 (1.5%)	15/202 (7.4%)	0/202
<u>Aspartate Aminotransferase (Aspartate aminotransferase increased)</u>	58/201 (28.9%)	6/201 (3.0%)	22/202 (10.9%)	1/202 (0.5%)
Bilirubin (Blood bilirubin increased)	25/203 (12.3%)	1/203 (0.5%)	29/203 (14.3%)	0/203

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute

Note: NCI grades were coded using CTCAE Version 5.

Note: Percentages are based on the number of patients with at least one post-baseline value available for that parameter.

Note: Post-baseline value is for on-treatment period only.

Note: A patient is counted only once for multiple occurrences for the same parameter.

Safety in special populations

Table 59: Overview of Treatment-Emergent Adverse Events by Age (<65, ≥65 to <75, ≥75) - (Safety Analysis Set)

	Cemiplimab (N = 205)			Placebo (N = 204)		
	Age			Age		
	<65 years (N = 54)	65 to <75 years (N = 80)	≥75 years (N = 71)	<65 years (N = 65)	65 to <75 years (N = 68)	≥75 years (N = 71)
TEAEs	53 (98.1%)	70 (87.5%)	64 (90.1%)	58 (89.2%)	61 (89.7%)	63 (88.7%)
TEAE with NCI grade 3/4/5	11 (20.4%)	16 (20.0%)	22 (31.0%)	7 (10.8%)	12 (17.6%)	10 (14.1%)
TE-SAEs	6 (11.1%)	12 (15.0%)	18 (25.4%)	2 (3.1%)	8 (11.8%)	9 (12.7%)
Treatment-related TEAEs	39 (72.2%)	46 (57.5%)	43 (60.6%)	30 (46.2%)	34 (50.0%)	30 (42.3%)
TEAE leading to study discontinuation	3 (5.6%)	6 (7.5%)	11 (15.5%)	0	1 (1.5%)	2 (2.8%)
TEAE leading to death	0	0	2 (2.8%)	0	0	2 (2.8%)
TEAE leading to study treatment interruption/delay	11 (20.4%)	16 (20.0%)	19 (26.8%)	7 (10.8%)	10 (14.7%)	9 (12.7%)

Abbreviations: NCI, National Cancer Institute; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event

Table 60: Overview of Treatment-Emergent Adverse Events by Gender (Male, Female) - (Safety Analysis Set)

	Cemiplimab (N = 205)		Placebo (N = 204)	
	Gender		Gender	
	Male (N = 171)	Female (N = 34)	Male (N = 172)	Female (N = 32)
TEAE	157 (91.8%)	30 (88.2%)	154 (89.5%)	28 (87.5%)
TEAE with NCI grade 3/4/5	41 (24.0%)	8 (23.5%)	23 (13.4%)	6 (18.8%)
TE-SAE	31 (18.1%)	5 (14.7%)	17 (9.9%)	2 (6.3%)
Treatment-related TEAE	109 (63.7%)	19 (55.9%)	80 (46.5%)	14 (23.8%)
TEAE leading to study treatment discontinuation	20 (11.7%)	0	2 (1.2%)	1 (3.1%)
TEAE leading to death	2 (1.2%)	0	1 (0.6%)	1 (3.1%)
TEAE leading to study treatment interruption/delays	34 (19.9%)	12 (35.3%)	20 (11.6%)	6 (18.8%)

Table 61: Overview of Treatment-Emergent Adverse Events by Region (North America, Australia/New Zealand, ROW) - (Safety Analysis Set)

	Cemiplimab (N = 205)			Placebo (N = 204)		
	Region			Region		
	North America (N = 37)	Australia/New Zealand (N = 87)	ROW (N = 81)	North America (N = 31)	Australia/New Zealand (N = 89)	ROW (N = 84)
TEAEs	35 (94.6%)	85 (97.7%)	67 (82.7%)	29 (93.5%)	85 (95.5%)	68 (81.0%)
TEAE with NCI Grade 3/4/5	9 (24.3%)	22 (25.3%)	18 (22.2%)	3 (9.7%)	18 (20.2%)	8 (9.5%)
TE-SAEs	7 (18.9%)	18 (20.7%)	11 (13.6%)	3 (9.7%)	10 (11.2%)	6 (7.1%)
Treatment-related TEAEs	24 (64.9%)	58 (66.7%)	46 (56.8%)	18 (58.1%)	50 (56.2%)	26 (31.0%)
TEAE leading to study discontinuation	4 (10.8%)	9 (10.3%)	7 (8.6%)	1 (3.2%)	0	2 (2.4%)
TEAE leading to death	0	1 (1.1%)	1 (1.2%)	0	1 (1.1%)	1 (1.2%)
TEAE leading to study treatment interruption/delay	8 (21.6%)	18 (20.7%)	20 (24.7%)	4 (12.9%)	10 (11.2%)	12 (14.3%)

Abbreviations: NCI, National Cancer Institute; ROW, Rest of the World; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event

Safety related to drug-drug interactions and other interactions

No new information is available on drug-drug interactions or other interactions.

Discontinuation due to adverse events

Table 62: Summary of Dose Delays and Infusion Interruptions (SAS) – Part 1

	Cemiplimab (N = 205)	Placebo (N = 204)
Participants with at least one dose delay or infusion interruption, n (%)	45 (22.0%)	23 (11.3%)
Participants with at least one dose delay, n (%)	41 (20.0%)	19 (9.3%)
Number of dose delays		
= 1	26 (12.7%)	15 (7.4%)
= 2	12 (5.9%)	4 (2.0%)
>2	3 (1.5%)	0
Participants with at least one infusion interruption, n (%)	5 (2.4%)	6 (2.9%)
Number of infusion interruptions		
= 1	4 (2.0%)	6 (2.9%)
= 2	1 (0.5%)	0
>2	0	0
Reasons for infusion interruption, n (%)		
AE	3 (1.5%)	3 (1.5%)
Others [1]	2 (1.0%)	3 (1.5%)

Table 63: Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation by System Organ Class Preferred Term, and NCI Grade (All, Grade ≥3) (SAS) – Part 1

System Organ Class, n (%)	Cemiplimab (N = 205)		Placebo (N = 204)	
Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of participants with at least one such TEAE	20 (9.8%)	16 (7.8%)	3 (1.5%)	2 (1.0%)
Skin and subcutaneous tissue disorders	4 (2.0%)	4 (2.0%)	0	0
Immune-mediated dermatitis	1 (0.5%)	1 (0.5%)	0	0
Pemphigoid	1 (0.5%)	1 (0.5%)	0	0
Rash	1 (0.5%)	1 (0.5%)	0	0
Skin ulcer	1 (0.5%)	1 (0.5%)	0	0
Investigations	3 (1.5%)	2 (1.0%)	0	0
Alanine aminotransferase increased	3 (1.5%)	2 (1.0%)	0	0
Aspartate aminotransferase increased	2 (1.0%)	1 (0.5%)	0	0
Blood alkaline phosphatase increased	2 (1.0%)	0	0	0
Gamma-glutamyl transferase increased	1 (0.5%)	0	0	0
Endocrine disorders	2 (1.0%)	2 (1.0%)	0	0
Adrenal insufficiency	2 (1.0%)	2 (1.0%)	0	0
Gastrointestinal disorders	2 (1.0%)	2 (1.0%)	0	0
Colitis	1 (0.5%)	1 (0.5%)	0	0
Immune-mediated enterocolitis	1 (0.5%)	1 (0.5%)	0	0
Musculoskeletal and connective tissue disorders	2 (1.0%)	1 (0.5%)	0	0
Arthralgia	1 (0.5%)	0	0	0
Myositis	1 (0.5%)	1 (0.5%)	0	0
Cardiac disorders	1 (0.5%)	1 (0.5%)	0	0
Myocarditis	1 (0.5%)	1 (0.5%)	0	0
General disorders and administration site conditions	1 (0.5%)	0	0	0
Fatigue	1 (0.5%)	0	0	0
Hepatobiliary disorders	1 (0.5%)	1 (0.5%)	0	0
Immune-mediated hepatitis	1 (0.5%)	1 (0.5%)	0	0
Infections and infestations	1 (0.5%)	1 (0.5%)	0	0
Urinary tract infection	1 (0.5%)	1 (0.5%)	0	0

Injury, poisoning and procedural complications	1 (0.5%)	0	0	0
Infusion related reaction	1 (0.5%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5%)	1 (0.5%)	3 (1.5%)	2 (1.0%)
Dedifferentiated liposarcoma	1 (0.5%)	1 (0.5%)	0	0
Acute myeloid leukaemia	0	0	1 (0.5%)	0
Hepatocellular carcinoma	0	0	1 (0.5%)	1 (0.5%)
Lung neoplasm malignant	0	0	1 (0.5%)	1 (0.5%)
Renal and urinary disorders	1 (0.5%)	1 (0.5%)	0	0
Acute kidney injury	1 (0.5%)	1 (0.5%)	0	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, Preferred Term; SOC, System Organ Class; TEAE, Treatment-emergent adverse event

Note: All adverse events were coded using MedDRA Version 27.0. NCI grades were coded using CTCAE Version 5.

Note: A patient is counted only once per the worst grade for multiple occurrences within a SOC/PT.

Note: For SOC, the table is sorted by decreasing frequency in the cemiplimab arm. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab arm.

Post marketing experience

The cumulative post-marketing exposure to cemiplimab is estimated to be 39,208 patient years. A total of 1939 patients have been treated with investigational cemiplimab monotherapy.

2.5.1. Discussion on clinical safety

Cemiplimab holds indications in metastatic cutaneous squamous cell carcinoma (mCSCC), metastatic basal cell carcinoma (BCC), metastatic cervical cancer and metastatic non-small cell lung cancer (mNSCLC). The existing safety profile in varied metastatic settings is well known and has been explored across multiple and large randomized studies compiling a reference monotherapy group (i.e. Monotherapy Pool) consisting of 1281 patients. As an immune-checkpoint inhibitor (PD-L1 antibody) cemiplimab exhibits known class effects characterized by immune-mediated adverse reactions.

The applicant presents new safety data from the pivotal trial 1788 where cemiplimab safety data is reported in an adjuvant setting for the first time. Overall safety methodology is acceptable. Two primary safety comparisons are presented; cemiplimab patients (n = 205) compared to placebo patients (n = 204) within the pivotal study 1788 and cemiplimab patients in the 1788 study compared to a composite monotherapy group enclosing patients given cemiplimab across 5 prior clinical studies (n = 1281) (i.e. the Monotherapy Pool). It is noted, that monotherapy/advanced setting group consists of patients receiving dosing regimens other than the 350mg Q3W and 700 Q6W after 12 weeks. However, the vast majority (~90%) of the monotherapy reference group received the 350mg Q3W and the safety comparison is acceptable.

Exposure was 47.9 weeks in the pivotal trial and 28.3 weeks in Monotherapy Pool, which is likely a result of the different settings (adjuvant vs. advanced/metastatic). Within the pivotal trial exposure was well balanced between placebo and cemiplimab with 47.7 vs. 47.9 weeks of exposure respectively. The median number of cycles in the cemiplimab group was 9. Mainly white males were exposed in study 1788, which is in line with known epidemiological risk factors for CSCC. In total, 34 females

(16.6%) were exposed to cemiplimab in study 1788 and cemiplimab exposure in females has been thoroughly explored in study 1676 (cervical cancer).

The **incidence of all grades TEAEs** was well balanced between the cemiplimab arm and the placebo arm (91.2% versus 89.2%) and although there was almost 10% more grade 3-5 treatment emergent adverse events (TEAEs) in the cemiplimab arm (23.9%), there was still a significant amount in the placebo arm (14.2%) most likely reflecting the high age of the population (median age ~70yr) and burden of comorbidities where >95% of the patient population has at least one medical history finding and >60% has a history of vascular disorder. An overall 10% difference between the groups is also reported in treatment-related AEs where 9.8% of the cemiplimab group experienced grade 3-5 events and only 0.5% experienced this in the placebo group.

Significant TEAE differences between cemiplimab and placebo were mainly observed in rash (16.1% vs 8.8%), peripheral oedema (5.4% vs. 2.5%) and hypothyroidism (11.7% vs. 2.9%). In the cemiplimab group 17.6% experienced TE-SAEs while the placebo group experienced 9.3%. These were most commonly pneumonia (1% in both groups), endocrine disorders (1.5% vs 0%) and gastrointestinal disorders (1.5% vs 0.5%). There was a difference between the incidence of low-grade psychiatric disorders between cemiplimab and placebo (8.3% vs. 6.9%), such as insomnia (5.4% vs. 2.5% in placebo patients). There was a similar incidence of medical history of insomnia and as such insomnia is not considered an ADR. Comparing **incidences of >grade 3 TEAEs** between the Monotherapy Pool (prior studies) and patients receiving cemiplimab in pivotal trial, patients in the pivotal trial experienced significantly more increased alanine aminotransferase (2.0% vs 0.5) and significantly less anaemia (0.5% vs 5.2%) and fatigue (1.0% vs. 2.6%).

The identified adverse drug reactions in the pivotal trial are in line with the ADR profile from the Monotherapy Pool as reflected in the SmPC. ADRs in the pivotal trial were of lower incidences except for hypo- and hyperthyroidism and low-grade (combined term) rash (36.6% vs 21.4%) and pruritus (16.1% vs. 12.7%), which were similar to previous trials with similar exposure (study 1540). Notably, low-grade rash and pruritus were also quite frequent in the placebo group (21.1% and 12.3%, respectively). It was not considered clinically relevant to pool safety data from an earlier setting of CSCC with safety data from advanced solid malignancies due to differences in the patient population by disease duration, stage, other treatments used and duration of exposure (47.9 weeks in Study 1788 and 28.3 weeks in Monotherapy Pool).

Adverse events of special interest included Infusion-related reactions (IRR) and immune-mediated adverse events (ImAE). IRRs incidence was 2.9% (all grades) and 0.5% (>grade 3) in the pivotal study compared to 3.3% (all grades) in the Monotherapy Pool. Incidence of **immune-mediated adverse events (imAEs)** were comparable between the pivotal trial and the Monotherapy Pool with a small increased incidence of hypothyroidism (>grade 3: 6.8% vs <0.1%) and hyperthyroidism (all grades: 5.4% vs. 3.0%). Incidences of pneumonitis (all grades: 2.0% vs. 2.6%, >grade 3: 0% vs 0.9%), hepatitis (all grades: 2.0% vs. 2.7%, >grade 3: 1.5% vs 1.8%) and colitis (all grades: 1.5% vs. 2.0%, >**grade 3**: 1.0% vs 2.0%) were all well balanced. Time to onset of first imAE was 2.0 months median in the cemiplimab group, which is comparable to literature review on the adverse effects of ICI treatments (median 6-14 weeks).

Significantly more patients in the cemiplimab arm (17.6%) experienced **serious TE-SAEs** than in the placebo arm (9.3%), but considerably lower than mCSCC patients in the Monotherapy Pool (~28%). TE-SAEs were distributed across various types of AEs with adrenal insufficiency, pneumonia and diarrhoea, which each constituted about 1% of cases. Two patients died from TEAEs in each group.

One 85-year-old male patient with multiple comorbidities died from treatment related myositis and hepatitis in the cemiplimab group.

In terms of laboratory abnormalities, 83.3% of patients in the cemiplimab arm and 78.3% of patients in the placebo arm experienced haematological laboratory abnormalities, here 7.9% and 5.4% were above grade 3 in each group respectively. Markedly, 7.4% of patients in the cemiplimab arm and 4.4% of patients in the placebo arm experienced >grade 3 decreased lymphocyte count. While, decreased lymphocytes are not expected to lead to significant clinical infection, there was a slightly higher rate of low grade upper respiratory tract infections in the cemiplimab arm vs placebo (11.2% vs 8.8), which was comparable to the Monotherapy Pool (10.9%). Liver parameters were significantly raised in the cemiplimab arm with 3.9% of patients having a grade >3 increased alanine aminotransferase (ALAT) vs 0% in the placebo arm, however only one patient in the cemiplimab arm experienced > grade 3 increased bilirubin vs. none in the placebo. Incidence of >grade 3 hepatitis in study 1788 were comparable to the Monotherapy Pool (1.5% vs 1.8%).

In the pivotal trial, 9.8% of CSCC patients **discontinued treatment due to TEAEs** with 7.8% of these being above grade 3 TEAEs. The most common cause of discontinuation was increased ALAT (1.5%) whereas pneumonitis, hepatitis and colitis were the most common TEAEs leading to discontinuations in the Monotherapy Pool. Across the studies included in the Monotherapy Pool the incidence of TEAEs leading to discontinuation was between 6.5% - 17.6%. In retrospective cohort studies with real-world data, the estimated discontinuation rate from anti PD1/-L1 irAEs is ~17% (Virtanan et al, 2024, [38398099](#)). In mCSCC patients (Study 1540), TEAEs led to permanent discontinuation of cemiplimab in 10.4% of cemiplimab patients with pneumonitis being the most common cause leading to discontinuation (3.1%). These differences between the pivotal trial and the monotherapy trials may be explained by the different settings in which the risks and consequences of discontinuation of treatment in metastatic disease are perceived as more severe by patients and their caregivers than in the adjuvant setting.

Analyses of the pivotal trial **special populations** showed that cemiplimab safety profile was worse in the older population with more TE-SAEs (19.9% vs. 11.1%) and more discontinuations (11.3% vs. 5.6%). Gender distribution followed the epidemiological trends with an imbalance towards males (171 vs 34 females), however there was a comparable number of TEAEs > grade 3 (24% vs. 23.5%, males vs. female) and slightly lower incidence of TE-SAEs among females (14.7% vs. 18.1%). Safety profiles by geographic regions showed a more favourable safety profile in rest-of-world (n=81) compared to Australia/New Zealand in cemiplimab and placebo treated patient with a large difference in TE-SAEs (20.7% vs. 13.6% in cemiplimab arms between regions and 11.2% vs. 7.1% in placebo arms between regions). These differences are considered a chance finding.

No novel safety signal was observed in the pivotal trial and key findings on safety are already reflected in the SmPC.

In line with the latest update to the excipient guideline, a warning was added in section 4.4 of the SmPC to highlight that L-proline may be harmful for patients with hyperprolinaemia type I or type II and that polysorbate 80 may cause allergic reactions.

2.5.2. Conclusions on clinical safety

The pivotal study 1788 provides safety data from 205 patients for cemiplimab in the adjuvant setting of CSCC. There were no major clinically significant deviations to the known safety profile.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports 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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.3 with the following content:

Safety concerns

Table 64: Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	imARs (pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis, and other imARs) IRRs
Important Potential Risks	Lack of effect due to anti-drug antibodies

Pharmacovigilance plan

All studies from RMP part III have been completed. There are no additional pharmacovigilance activities planned for this product.

Risk minimisation measures

Table 65: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Activities	Proposed Pharmacovigilance Activities
Important Identified Risk: Immune-mediated Adverse Reactions Immune-mediated adverse reactions (immune-mediated pneumonitis, colitis,	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: See SmPC sections 4.2 and 4.4 See PL sections 2 and 3	Routine pharmacovigilance Use of specific follow-up questionnaire for spontaneous

Safety Concern	Risk Minimisation Activities	Proposed Pharmacovigilance Activities
hepatitis, endocrinopathies, immune-mediated skin reactions, nephritis, and other imARs)	Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is supplied 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 Alert Card	postmarketing reports of imARs
Important Identified Risk: Infusion-related Reactions	Routine 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, 4.3, and 4.4. PL sections 2 and 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is supplied 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 Alert Card	Routine pharmacovigilance Use of specific follow-up questionnaire for spontaneous post-authorisation reports of infusion-related reactions
Important Potential Risk: Lack of Effect due to Anti-drug Antibodies	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.	Routine pharmacovigilance

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Annex IID of the PI has been updated.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc...], which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

This variation is not related to a change in legal status or to a new presentation, and no particular critical safety issues have been identified with Libtayo. Therefore, as per the "Guideline on the readability of the labelling and package leaflet of medicinal products for human use", a new consultation with target patient groups for the package leaflet is not considered mandatory nor necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

LIBTAYO as monotherapy is indicated for the adjuvant treatment of adult patients with CSCC at high risk of recurrence after surgery and radiation (see section 5.1 for selection criteria).

3.1.2. Available therapies and unmet medical need

The majority of early stage CSCCs are curable with the local therapy (surgery, radiation therapy, photodynamic therapy and other local therapies). The cure rate of CSCC managed by surgery is approximately 95% (Breuninger, 2013). Patients with locoregional recurrence not amenable for the rescue with surgery or RT or patients with distant metastasis constitute therapeutic challenge. The only EU approved treatment for this population is cemiplimab.

For patients at high risk of CSCC recurrence after curative intent local modality treatment, there are no approved adjuvant treatment options. Therefore, there is an unmet medical need for an effective treatment option with an acceptable safety profile in patients at a high-risk of CSCC recurrence after surgery and post-operative RT to maintain the cure achieved with local therapies and prevent disease recurrence.

3.1.3. Main clinical studies

Study 1788 is an ongoing, Phase III, randomized 1:1, double-blind, placebo-controlled, 2-arm, multi-center, international study to assess the efficacy and safety of cemiplimab monotherapy compared to placebo as adjuvant treatment in patients who have completed surgery and adjuvant radiotherapy (RT) for CSCC and have at least 1 criterion that puts them at high risk for recurrence of CSCC. The study consists of two parts: part 1 (blinded, figure 1) and optional part 2 (open-label), where patients could receive cemiplimab for up to 96 weeks after disease recurrence. The results of cemiplimab vs. placebo arms from the part 1 of study 1788 form the basis for this submission.

3.2. Favourable effects

At the first interim analysis, the study 1788 met its primary endpoint, demonstrating improvement in DFS with cemiplimab over placebo in the ITT Population (HR: 0.32; 95% CI: 0.20, 0.51; p value < 0.0001). Updated DFS results (DCO 07 Apr 2025) yield similar results with HR 0.354 [95%CI: 0.354 (0.229, 0.548); p value <0.0001]. Numerically fewer deaths have been observed in the cemiplimab arm vs the placebo arm (15 vs 18).

3.3. Uncertainties and limitations about favourable effects

OS data are immature at the time of the DCO. Updated OS data together with updated descriptive DFS will be provided post-approval (REC).

3.4. Unfavourable effects

The overall **incidence of all grades TEAEs** was 91.2% in the cemiplimab arm versus 89.2% in the placebo arm. Main TEAE differences were observed in rash (16.1% vs 8.8%), peripheral oedema (5.4% vs. 2.5%) and hypothyroidism (11.7% vs. 2.9%). Compared to the Monotherapy Pool, low grade rash and pruritus (combined terms) were higher in the pivotal trial patients (36.6% vs 21.4% and 16.1% vs. 12.7%, respectively).

Patients receiving cemiplimab in the pivotal trial experienced higher frequencies of **>grade 3** increased alanine aminotransferase (2.0% vs 0.5) and diarrhoea (1.5% vs 0.7%) compared to the Monotherapy Pool. In the Cemiplimab group, 17.6% experienced **TE-SAEs** while the placebo group experienced 9.3% and ~28% of patients experienced these in the Monotherapy Pool. In this pivotal trial, TE-SAEs were most commonly pneumonia (1%), endocrine disorders (1.5%) and gastrointestinal disorders (1.5%). There was also a higher incidence of low-grade psychiatric disorders between Cemiplimab and placebo (8.3% vs. 6.9%), mainly driven by insomnia (5.4% vs. 2.5% in placebo patients), which is not currently acknowledged as an ADR in monotherapy treatment.

Adverse events of special interest included Infusion-related reactions (IRR) and immune-mediated adverse events (ImAE). IRRs incidence was 2.9% (all grades) and 0.5% (>grade 3) in the pivotal study compared to 3.3% (all grades) in the Monotherapy Pool. Incidence of **immune-mediated adverse events (imAEs)** were comparable between the pivotal trial and the Monotherapy Pool with an increased incidence of hypothyroidism (all grades: 10.7% vs. 6.8%, >grade 3: 0.5% vs <0.1%) and hyperthyroidism (all grades: 5.4% vs. 3.0%). The Incidences of important known ImAEs for cemiplimab were: Pneumonitis (all grades: 2.0%, >grade 3: 0%), hepatitis (all grades: 2.0%, >grade 3: 1.5%) and colitis (all grades: 1.5%, >grade 3: 1.0%). Time to onset of first imAE was 2.0 months median in the Cemiplimab group.

There were four **deaths from TEAEs**, two in each group, only one was related to cemiplimab.

In the pivotal trial, 9.8% of CSCC patients **discontinued treatment due to TEAEs** with 7.8% of these being above grade 3 TEAEs. Increased ALAT (1.5%) was the most common cause whereas pneumonitis, hepatitis and colitis were the most common TEAEs leading to discontinuations in the Monotherapy Pool. In mCSCC patients (Study 1540) pneumonitis was the most common cause leading to discontinuation (3.1%).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 66: Effects Table for Libtayo for adjuvant CSCC (data cut-off: 04 Oct 2024)

Effect	Short description	Unit	Treatment Cemiplimab N=209	Control Placebo N=206	Uncertainties / Strength of evidence	References
Favourable Effects						
DFS by INV (ITT)	Disease-free survival by Investigator	Median DFS in months (95% CI) HR (95%CI)	NR (NE, NE) 0.32 (0.20, 0.51)	49.4(48.5, NE)	Assessed by INV, RECIST criteria not used Median FU 18.3 months Updated results with Median FU 30 months DCO 07 Apr 2025: 0.354 (0.229, 0.548)	CSR
Unfavourable Effects						
AEs, Grade 3 or higher	Incidence of AE grade 3 or higher	Proportion (%)	23.9	14.2		
SAEs	Incidence of serious adverse events	Proportion (%)	17.6	9.8		
AEs leading to discontinuation	Incidence of discontinuations due to adverse events	Proportion (%)	9.8	1.5		
Nephritis (>3 grade)	Common adverse event and AESI	Proportion (%)	0.5	0		
Colitis (>3 grade)	Common adverse event	Proportion (%)	1.0	0		
Hepatitis (>3 grade)	Common adverse event	Proportion (%)	1.5	0		
Deaths	Deaths due to AEs	Proportion (%)	1	1		

Abbreviations: INV: investigator, CI: Confidence interval; DFS: Disease-free survival; HR: Hazard ratio; N: Number of patients enrolled; NE: Not evaluated; NR: Not reached

Notes: Results from IA 1=primary analysis

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study 1788 showed, at the first pre-specified interim analysis, a statistically significant improvement in DFS by INV in all participants. The updated results provide some reassurance that the DFS benefit observed in the primary analysis is maintained with longer follow-up, despite the fact that the expected plateau of KM curves is not reached yet. In conclusion, with some uncertainties related to the long-term follow-up, the results of study 1788 are statistically and clinically relevant for patients at the high risk of recurrence of CSCC after surgery and radiotherapy.

Cemiplimab treatment is associated with a high rate of serious adverse events (17.6%), a risk of severe immune-mediated toxicity underlined by the fact that one patient died from myositis in the pivotal trial. Moreover, one third of patients experienced rash and one in four experienced fatigue. This is in line with the known safety profile of cemiplimab and considered acceptable in this treatment setting.

3.7.2. Balance of benefits and risks

Based on early interim analysis, the results of study 1788 overall support the sought indication of cemiplimab as adjuvant treatment in patients at high risk of recurrence after surgery and radiotherapy for CSCC, showing a statically significant improvement in DFS with an acceptable safety profile. The B/R balance can be considered positive.

3.7.3. Additional considerations on the benefit-risk balance

To highlight to the prescribers the studied population, a reference directing to the selection criteria described in SmPC section 5.1 was added in the final wording of the indication.

3.8. Conclusions

The overall B/R of Libtayo is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, and IIIB

Extension of indication to include treatment of adjuvant treatment of adult patients with Cutaneous Squamous Cell Carcinoma (CSCC) at high risk of recurrence after surgery and radiation for LIBTAYO,

based on interim results from study R2810-ONC-1788; this is a phase 3, randomized, placebo-controlled, double-blind study of adjuvant cemiplimab versus placebo after surgery and radiation therapy in patients with high risk CSCC; As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.3 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the warnings for the excipients proline and polysorbate to reflect EU guidance (Section 4.4) and also updated Annex IID of the PI in line with the updates made to the RMPv4.3 to consolidate the aRMMs.

Amendments to the marketing authorisation

In view of the data submitted with the variation procedure><grouped worksharing procedures>, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

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.

In addition, 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 card**

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

- 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.