

Cemiplimab (cutaneous squamous cell carcinoma, adjuvant)

Benefit assessment according to §35a SGB V¹

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0

Fax: +49 221 35685-1

Email: info@iqwig.de

Internet: www.iqwig.de

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Medical and scientific advice

- Jochem Potenberg, Ev. Waldkrankenhaus, Berlin, Germany

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Patient and family involvement

No feedback was received within the framework of this dossier assessment.

IQWiG employees involved in the dossier assessment

- Nina Castor
- Anna-Katharina Barnert
- Tobias Effertz
- Tatjana Hermanns
- Michaela Florina Kerekes
- Judith Kratel
- Mattea Patt
- Volker Vervölgyi
- Pamela Wronski

Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AWMF	Association of the Scientific Medical Societies
CLL	chronic lymphocytic leukaemia
cSCC	cutaneous squamous cell carcinoma
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITM	in-transit metastases
MRI	magnetic resonance imaging
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PT	Preferred Terms
RCT	randomized controlled trial
SAE	serious adverse event
SmPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug cemiplimab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the ‘company’). The dossier was sent to IQWiG on 15 December 2025.

Research question

The aim of this report is to assess the added benefit of cemiplimab compared with watchful waiting as the appropriate comparator therapy (ACT) in adult patients with cutaneous squamous cell carcinoma (cSCC) at high risk of recurrence after surgery and radiation.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of cemiplimab

Therapeutic indication	ACT ^a
Adult patients with cutaneous squamous cell carcinoma at high risk of recurrence after surgery and radiation; adjuvant treatment ^b	Watchful waiting
a. Presented is the ACT specified by the G-BA. b. It is assumed that patients have undergone an R0 resection or have achieved a complete radiological response. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA’s specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company’s inclusion criteria.

Study pool and study design

Concurring with the company, the study pool of this benefit assessment comprises the C-POST study. The C-POST study is an ongoing, double-blind, multicentre RCT comparing cemiplimab as monotherapy with placebo, in each case following surgery and subsequent radiation. The study included adult patients with cSCC at high risk of recurrence who had previously undergone surgery and completed post-operative radiation with curative intent.

The study included patients who, in accordance with the inclusion criteria, met at least one of the following criteria for high-risk cSCC: lymph node involvement (nodal disease), in-transit metastases (ITM), T4 lesion (head and neck tumour and non-head and neck tumour), perineural invasion or local recurrence.

Furthermore, at the time of inclusion, patients had to be in good general health, with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Radiotherapy had to have been administered at a minimum dose of 50 Gray (Gy), within 4 to 6 weeks of surgery and 2 to 10 weeks prior to randomization. Patients who had previously undergone chemoradiotherapy were also eligible for inclusion.

Patients who had previously received systemic immunotherapies (e.g. with programmed cell death ligand 1 [PD-(L)1] inhibitors) for cSCC or other immunomodulatory cancer treatments, who had been administered immunosuppressive corticosteroids (at a dose of > 10 mg prednisone or prednisone equivalents) within 4 weeks prior to administration of the first study medication, or who had previously undergone an organ transplant.

A total of 415 patients were included in the study and assigned in a 1:1 ratio to the intervention arm (N = 209) or the comparator arm (N = 206). Randomization in the C-POST study was stratified by anatomical region of the resected high-risk tumour (head and neck region vs. non-head and neck region), geographical region (North America vs. Australia/New Zealand vs. rest of the world), high-risk category (nodal vs. non-nodal), ECOG PS (0 vs. 1) and a history of chronic lymphocytic leukaemia (CLL) (present vs. absent).

The C-POST study comprises two phases: phase 1 of the study addresses the double-blind, direct comparison of cemiplimab versus placebo. Phase 2 of the study is unblinded and optional. In Phase 2, patients from Phase 1 with confirmed recurrence may receive 96-week treatment with cemiplimab, regardless of which arm they were assigned to in Phase 1. Patients who were randomized to the intervention arm in Phase 1 could only receive cemiplimab again in Phase 2 if the recurrence had occurred no earlier than 3 months after the completion of the 48-week treatment.

In Phase 1 of the study, cemiplimab was administered in accordance with the Summary of Product Characteristics (SmPC). According to the original protocol, 350 mg of cemiplimab were administered every 3 weeks over a 48-week period. Under Protocol Amendment 2 of 29 June 2021, the dosing regimen was adjusted and 350 mg of cemiplimab were administered every 3 weeks over a 12-week period (4 doses of the study medication), followed by 700 mg of cemiplimab every 6 weeks for a further 36 weeks (6 doses). Both dosing regimens are in accordance with the SmPC. Treatment was continued until the end of the planned 48-week treatment period, until recurrence, unacceptable toxicity or withdrawal of consent. For the purposes of blinding, a placebo corresponding to the intervention was administered in the

comparator arm. Treatment of adverse events (AEs) or immune-mediated AEs, including the administration of systemic corticosteroids, was permitted in both arms.

Primary outcome of the C-POST study was disease-free survival (DFS). Secondary outcomes were overall survival and outcomes of the categories morbidity, health-related quality of life and side effects.

Uncertainties in the C-POST study

Risk classification for the high risk of recurrence

In accordance with the inclusion criteria, the following risk factors for a high risk of recurrence were identified:

- nodal disease with extracapsular extension and at least one lymph node > 20 mm in the pathological findings and/or ≥ 3 positive lymph nodes in the surgical pathology report
- ITM, defined as skin or subcutaneous metastases located > 2 cm from the primary cSCC tumour but not extending beyond the regional lymph node station
- T4 tumour, including head and neck tumour and non-head and neck tumour
- perineural invasion, defined as clinical and/or radiological involvement of the nerves
- recurrent cSCC, defined as cSCC occurring within the area of the previously resected tumour (with additional characteristics such as, for example, poorly differentiated histology or stage $\geq$ N2b disease)

According to the S3 guideline 'Actinic keratosis and squamous cell carcinoma of the skin', issued by the Association of the Scientific Medical Societies (AWMF), there is generally no uniform classification system for identifying patients as having high-risk cSCC. Overall, the following key risk factors can be identified, although it is unclear how the individual factors should be weighted:

- Tumour diameter > 20 mm
- Infiltration depth > level 3
- De-differentiation
- Perineural invasion
- Location: ear and lower lip
- Immunosuppression
- Histological tumour thickness > 6 mm
- Desmoplasia

The risk factors selected by the company deviate from those set out in the S3 guideline. Furthermore, no information is available on certain characteristics, such as tumour thickness, either in the dossier or in the study documentation.

For this research question, all patients were required to have undergone prior surgery and adjuvant radiotherapy. According to the guidelines, adjuvant radiotherapy is not recommended as standard, but only in the presence of certain risk factors for recurrence. The S3 guideline recommends adjuvant radiotherapy for:

- R1 or R2 resection and the inability to perform a re-excision
- Extensive lymph node involvement (> 1 affected lymph node, a lymph node metastasis > 3 cm or a breach of the capsule)
- Intraparotid lymph node involvement
- Extensive perineural sheath infiltration

The criteria selected by the company to characterize a high risk of recurrence therefore largely represent the factors for which adjuvant radiotherapy is recommended according to the guidelines. It can therefore be assumed that, despite the deviations from the factors for high-risk cSCC listed in the guideline, the patient population in the C-POST study adequately represents the patient population of this research question.

Presence of an R0 resection or complete radiological response

In accordance with its information on the ACT, the G-BA assumes that patients have undergone an R0 resection or have achieved a complete radiological response. In accordance with the inclusion criteria, the patients had undergone macroscopic surgery for a pathologically confirmed cSCC prior to the start of the study. The dossier does not provide any information on the number of patients who underwent an R0 resection or achieved complete radiological response at baseline. The European Public Assessment Report (EPAR) published by the European Medicines Agency (EMA) contains data from a post-hoc analysis on the type of resection performed in patients with stage T3, T4, T4a and T4b tumour sizes. 46.9% of all the randomized patients in the intervention arm and 45.1% in the comparator arm had one of these tumour stages. Around 46% of these patients in the intervention arm and around 49% in the comparator arm underwent an R0 resection. In relation to all randomized patients, it is known that only 21.5% in the intervention arm and 22.3% in the control arm underwent an R0 resection. Around 45% of patients in the intervention arm underwent an R1 resection, compared with around 41% in the comparator arm. It is also known that, in relation to the total population, 21.1% of patients in the intervention arm and 18.4% in the comparator arm underwent an R1 resection at tumour sizes $\geq$ T3. In approximately 9% of patients with tumour

sizes $\geq T3$, it was not possible to evaluate the result of the surgery. The EPAR also provides no data on radiological response.

This research question addresses a group of patients who have undergone both surgery and adjuvant radiotherapy. As described, adjuvant radiotherapy is only recommended where a combination of specific risk factors is present. An R1-resection is a factor for which adjuvant radiotherapy is recommended in accordance with the S3 guideline. The fact that an R0 resection has not been performed does therefore not mean that the patients are not covered by this research question.

The guidelines do not include any recommendations for monitoring response following adjuvant radiotherapy that go beyond the superordinate follow-up recommendations. It can therefore be assumed that the success of adjuvant radiotherapy is reflected in the absence of at least early recurrence. Furthermore, due to various factors, an assessment of the radiological response is difficult immediately after radiation has been completed. For example, oedema and inflammatory processes can make imaging more difficult. The S3 guideline does not contain any direct recommendation regarding the radiation dose for post-operative radiotherapy. However, there are references in the literature to post-operative radiation with a total dose of 50 to 60 Gy. Patients in the C-POST study had to receive a radiation dose of at least 50 Gy in accordance with the inclusion criteria. The majority of patients (76% in both treatment arms) received a radiation dose of 60 to 69 Gy.

Given that adjuvant radiotherapy is only carried out in the presence of certain risk factors, for example in patients who have undergone R1 resection, and given that the patients in the study were treated with an adequate dose of radiation, it is assumed that the study population is sufficiently representative of the research question, even though no specific details are available regarding the surgery and radiotherapy undertaken prior to enrolment in the study.

Permitted radiochemotherapy following surgery

In accordance with the inclusion criteria, concomitant chemoradiotherapy was permitted following surgery. Adjuvant chemoradiotherapy is not covered by the present research question. Information on how many patients received chemoradiotherapy this is not available. However, the study report does provide data on the proportion of patients who received systemic therapy for the treatment of cSCC prior to study inclusion. The proportions were comparable, at 3.3% in the intervention arm and 6.3% in the control arm, and were low overall. Consequently, the use of chemoradiotherapy as an adjuvant treatment has no consequences for the benefit assessment.

Implementation of watchful waiting in the study

The G-BA specified watchful waiting as the ACT. In the C-POST study presented by company, patients in the comparator arm were no longer actively treated for their high-risk cSCC

following surgery and radiation, but were instead given a placebo corresponding to the intervention. The aim in both treatment arms was to provide individually optimized and supportive treatment to alleviate symptoms.

The following examinations were performed for assessing the health status or detecting recurrences in the C-POST study:

- A full physical examination upon screening, during the study treatment at the start of Cycles 2 to 4, and at the end of the treatment phase. Additionally, limited physical examinations were carried out at shorter intervals. As part of the follow-up, a full physical examination is carried out every 4 months during the first and the second year, and every 6 months from the third year onwards.
- Imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) during the planned 48-week treatment period, upon screening and at the end of each 12-week cycle, as well as every 4 months during the first 2 years of the planned follow-up and subsequently every 6 months until recurrence, death or the end of the study. Additional earlier imaging is possible at the investigator's discretion.
- histological or cytological confirmation of recurrence by means of a biopsy (unless the investigator considers a biopsy to pose an unacceptable safety risk, e.g. in the case of brain lesions)

The examinations performed in the C-POST study largely follow the guideline recommendations. The AWMF states that approx. 80% of recurrences occur within the first two years following the primary diagnosis and recommends close follow-up at three-month intervals during the first two years for patients at high risk of recurrence, followed by follow-up at three- to six-month intervals from the third to the fifth year, and thereafter, depending on the risk profile, follow-up at intervals ranging from 3 months to once a year, comprising a physical examination, lymph node sonography and imaging techniques (such as CT or MRI) if a recurrence is suspected.

Data cuts

In accordance with the study protocol, three further interim analyses were conducted following the amendment to the study protocol dated 29 June 2021 (Amendment 2) in addition to the originally planned final analysis at approximately 165 DFS events in the total population: after approximately 83 DFS events (50% of 165 DFS events), after around 107 (65%) and after around 132 DFS events (80%). The company presents analyses on 2 data cuts in Module 4 A of the dossier. The first data cut of 4 October 2024 represents the prespecified interim analysis of 50% of the DFS events in the total population. At the time of the data cut, 89 DFS events had occurred. The second data cut (the most recent data cut of 7 April 2025) is a non-prespecified data cut involving 97 DFS events (approx. 59%). The date of the second

data cut coincides with the submission of the documents of marketing authorization procedure to the EMA on 7 April 2025. It can therefore be assumed that this data cut was not requested by the EMA. The results of the first data cut were used for this benefit assessment.

Risk of bias

The risk of bias across outcomes is rated as low for the C-POST study.

The risk of bias is rated as low for the outcomes overall survival and failure of the curative treatment approach.

There is a high risk of bias for the outcomes on symptoms and health-related quality of life (each recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) and on health status (recorded with the Visual Analogue Scale of the European Quality of Life-5 Dimensions [EQ-5D VAS]). The risk of bias was rated as high for the outcomes serious AEs (SAEs), severe AEs, immune-mediated SAEs, immune-mediated severe AEs and hypothyroidism (Preferred Term [PT], AEs). Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited.

No suitable data available for the benefit assessment due to the observation period being too short

The follow-up duration of the C-POST study does not adequately cover the high-risk period for recurrence following the completion of treatment with cemiplimab. Thus, based on the results of the first data cut, there are no suitable data available to carry out an overall assessment of the positive and negative effects across all outcome categories in the current situation. This will be explained below, taking into account the present data situation.

In this therapeutic indication, curative therapy is generally possible and the aim of treatment. Recurrence following tumour resection and subsequent radiation means that the curative treatment approach has failed.

In order to meaningfully assess the failure of the curative treatment approach, it is generally necessary to carry out a sufficiently long follow-up period. This should, on the one hand, cover the high-risk period and, on the other hand, extend for a sufficiently long time beyond the end of treatment. This is intended to ensure that, once treatment is discontinued, relapses are actually prevented rather than merely delayed. According to the S3 guideline, most relapses in this therapeutic indication occur within the first two years after the primary diagnosis; intensified follow-up is therefore recommended during this period.

Information on the follow-up durations for patients in the C-POST study who had not experienced a DFS event by the date of the data cut is not available, but can be roughly

classified based on the following data: The maximum follow-up durations for the first randomized person was approximately 64 months. The minimum possible follow-up duration for the last randomized person was approximately 2 months. Although the median follow-up period for the entire study duration was 24 months, this means that 50% of patients were followed up for a shorter period. Overall, based on the available data, it is assumed that the follow-up period after the end of the maximum 48-week adjuvant therapy with cemiplimab is not sufficiently long for a relevant proportion of patients without DFS event to reliably rule out recurrences following the discontinuation of treatment. This assessment is also supported by the fact that the Kaplan-Meier curve of the intervention arm does not yet appear to have reached a stable plateau in terms of DFS. Even after the end of treatment with cemiplimab, a relevant extent of events continue to occur. The Kaplan-Meier curves also show that a large proportion of patients were censored at an early time point. Before the background of the follow-up periods listed above, it can be assumed that these were predominantly cases of administrative censoring. Due to the large number of early censorings, the data could be interpreted meaningfully.

Failure of the curative treatment approach is the essential treatment goal in this therapeutic indication. As it is not possible to draw reliable conclusions for this outcome at the time of the first data cut, a sufficient overall assessment of the positive and negative effects across all outcome categories cannot be performed.

The EPAR indicates that, as part of its scientific advice, the EMA has recommended using a fixed follow-up period for the data analysis rather than an event-driven follow-up period in this therapeutic indication. The company was advised to choose an analysis period for which the risk of recurrence in both arms is considered to be low. The EMA proposed a period of three years for this. This constitutes a sensible study design in the present situation. However, the company did not follow this proposal. Originally, only the primary analysis on DFS after 161 DFS events was planned. A total of three new interim analyses were added with Protocol Amendment 2. With 89 DFS events that occurred, the data cut used comprises around 50% of the originally planned number of events for the primary analysis. The EMA comments on the data submitted by the company pertaining to the recurrences in the two data cuts performed to date, noting that, given the duration of the observation period, there is still uncertainty as to whether the occurrence of recurrences is being prevented or merely delayed. For this reason, the EMA recommends that further descriptive data on DFS be submitted, as well as the final analysis on overall survival after the marketing authorization.

In summary, the data are currently unsuitable to allow for an overall assessment of the positive and negative effects of cemiplimab compared with the ACT across all outcome categories.

There are no suitable data available to assess the added benefit of cemiplimab compared with the ACT in adult patients with cSCC at high risk of recurrence after surgery and radiation. There is no hint of an added benefit of cemiplimab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

Table 3 shows a summary of probability and extent of the added benefit of cemiplimab.

Table 3: Cemiplimab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with cutaneous squamous cell carcinoma at high risk of recurrence after surgery and radiation; adjuvant treatment ^b	Watchful waiting	Added benefit not proven ^c
a. Presented is the ACT specified by the G-BA. b. It is assumed that patients have undergone an R0 resection or have achieved a complete radiological response. c. Only patients with an ECOG PS of 0 or 1 were included in the C-POST study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS $\geq$ 2. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that by the company, which derived an indication of a major added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

³ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) 'proof', (2) 'indication', (3) 'hint', or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or lesser benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of cemiplimab compared with watchful waiting as the ACT in adult patients with cSCC at high risk of recurrence after surgery and radiation.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of cemiplimab

Therapeutic indication	ACT ^a
Adult patients with cutaneous squamous cell carcinoma at high risk of recurrence after surgery and radiation; adjuvant treatment ^b	Watchful waiting
a. Presented is the ACT specified by the G-BA. b. It is assumed that patients have undergone an R0 resection or have achieved a complete radiological response. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

RCTs were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on cemiplimab (status: 4 November 2025)
- Bibliographical literature search on cemiplimab (last search on 04 November 2025)
- Search of trial registries / trial results databases for studies on cemiplimab (last search on 20 November 2025)
- Search on the G-BA website for cemiplimab (last search on 4 November 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on cemiplimab (last search on 19 December 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: cemiplimab vs. watchful waiting

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed	Sponsored study ^a	Third-party study	CSR	Registry entries ^b	Publication and other sources ^c
	(yes/no)	(yes/no)	(yes/no)	(yes/no [citation])	(yes/no [citation])	(yes/no [citation])
R2810-ONC-1788 (C-POST ^d)	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6,7]
a. Study sponsored by the company. b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries. c. Other sources: documents from the search on the G-BA website and other publicly available sources. d. In the following tables, the study is referred to by this acronym. G-BA: Federal Joint Committee; RCT: randomized controlled trial						

The study pool for this benefit assessment consists of the RCT C-POST. This concurs with the company's study pool.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: cemiplimab versus placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
C-POST	RCT, double-blind, parallel	Adult patients with cSCC at high risk of disease recurrence ^b after surgery ^c and radiation ^d ▪ ECOG PS ≤ 1	Cemiplimab (N = 209) placebo (N = 206)	Screening: 28 days treatment: 48 weeks or until premature discontinuation due to recurrence, unacceptable toxicity or withdrawal of consent follow-up observation ^e : until recurrence ^f , death, withdrawal of consent or end of the study ^g	107 study centres in Australia, Belgium, Brazil, Canada, France, Germany, Greece, Ireland, Italy, Japan, New Zealand, Poland, Russia, Spain, United Kingdom, United States 06/2019–ongoing data cuts: ▪ 04 October 2024 ^h ▪ 07 April 2025 ⁱ	Primary: DFS secondary: overall survival, morbidity, health-related quality of life, AEs
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. High-risk cSCC is defined as having at least one of the specified risk factors; see the text below. c. Surgery for a pathologically confirmed cSCC (primary cSCC lesion only, primary cSCC with lymph node involvement, or cSCC-nodal metastases with a known primary cSCC that has previously been treated within the draining lymph node region), with macroscopic surgery of all lesions. d. Post-operative radiation should be administered within 4 to 6 weeks of the surgery and completed within 2 to 10 weeks prior to randomization. Concurrent chemoradiotherapy is also permitted. Minimum biologically equivalent dose (BED) of 50 Gy at the site of the previous disease (for primary head and neck sites and non-head and neck sites). e. Outcome-specific information is described in Table 8.						

Table 6: Characteristics of the included study – RCT, direct comparison: cemiplimab versus placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
f. Following a recurrence, patients may, subject to certain criteria being met, opt to receive cemiplimab in the unblinded Phase 2 of the study (comparator arm), or resume treatment with cemiplimab about ≥ 3 months after the end of treatment (intervention arm). g. The study is scheduled to end once the primary analysis and the secondary overall survival analysis (approximately 24 months after the primary DFS analysis) have been completed, and the last patient has completed all treatment periods, including the 90-day follow-up. h. Primary analysis for the outcome DFS, as prespecified in Amendment 2 to the study protocol dated 29 June 2021, planned following approx. 83 events in the total population (50% of 165 DFS events); 89 DFS events had occurred by the time of the data cut (see Section I 3.2). i. Unspecified data cut for the outcome DFS; at the time of the data cut, 97 DFS events had occurred in the total population (59% of 165 DFS events) (see Section I 3.2). AE: adverse event; cSCC: cutaneous squamous cell carcinoma; DFS: disease-free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Gy: Gray; N: number of randomized patients; RCT: randomized controlled trial						

Table 7: Characteristics of the intervention – RCT, direct comparison: cemiplimab versus placebo

Study	Intervention	Comparison
C-POST	Cemiplimab 350 mg every 3 weeks, IV (4 doses) followed by cemiplimab 700 mg every 6 weeks^a, IV (6 doses) Dose modification: - dose modifications not allowed - dose interruption is permitted in the event of toxicity^b, largely in accordance with the summary of product characteristics (SmPC) Disallowed prior treatment - participation in a study with an investigational product or device within 4 weeks of the randomization date, or five half-lives (whichever is longer) - systemic anti-cancer immunotherapy for cSCC (e.g. CTLA-4, 4-1BB (CD137) or OX-40 inhibitors, therapeutic vaccines, anti-PD-1/PD-L1 or PI3Kδ inhibitors) - immunosuppressive corticosteroid doses (> 10 mg/day of prednisone or equivalent) within 4 weeks prior to the first dose of cemiplimab / placebo^c - treatment with an approved systemic tumour therapy^d within 4 weeks of the randomization date - allogeneic or autologous stem cell transplantation (SCT) - organ transplantation non-permitted concomitant treatment^e - tumour treatment other than the one used in the study - PD-1/PD-L1 inhibitors - radiation treatment allowed concomitant treatment - treatment of AEs / immune-mediated AEs, including systemic corticosteroids - systemic corticosteroids for physiological replacement therapy (including > 10 mg/day of prednisone or equivalent), or a short-term corticosteroid treatment for prophylaxis - surgical resection of premalignant or BCC lesions	Placebo IV every 3 weeks (4 doses) followed by placebo IV every 6 weeks (6 doses)
a. Dosing regimen amended in Protocol Amendment 2 (29 June 2021). In the original protocol, the plan was to administer 350 mg of cemiplimab every 3 weeks up to Week 48. b. In the event of interruptions of ≥ 84 days due to toxicity, the study treatment should be permanently discontinued. c. Short-term steroid treatment (e.g. prophylaxis for imaging techniques due to hypersensitivity to contrast agents), or steroids for physiological replacement therapy (i.e. adrenal insufficiency), are not excluded. d. Bisphosphonates or denosumab are not ruled out. AE: adverse event; BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; 4-1BB (CD137): 4-1BB antigen (cluster of differentiation 137 antigen); IV: intravenous; OX-40: cluster of differentiation 134 antigen; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; PI3Kδ: phosphatidylinositol-3-kinase delta; RCT: randomized controlled trial		

Study design

The C-POST study is an ongoing, double-blind, multicentre RCT comparing cemiplimab as monotherapy with placebo, in each case following surgery and subsequent radiation. The

study included adult patients with cSCC at high risk of recurrence who had previously undergone surgery and completed post-operative radiation with curative intent.

The study included patients who, in accordance with the inclusion criteria, met at least one of the following criteria for high-risk cSCC: lymph node involvement (nodal disease), ITM, T4 lesion (head and neck tumour and non-head and neck tumour), perineural invasion or local recurrence.

Furthermore, at the time of inclusion, patients had to be in good general health, with an EGOG PS of 0 or 1. Radiotherapy had to have been administered at a minimum dose of 50 Gray (Gy), within 4 to 6 weeks of surgery and 2 to 10 weeks prior to randomization. Patients who had previously undergone chemoradiotherapy were also eligible for inclusion.

Patients who had previously received systemic immunotherapies (e.g. with PD-(L)1 inhibitors) for cSCC or other immunomodulatory cancer treatments, who had been administered immunosuppressive corticosteroids (at a dose of > 10 mg prednisone or prednisone equivalents) within 4 weeks prior to administration of the first study medication, or who had previously undergone an organ transplant.

A total of 415 patients were included in the study and assigned in a 1:1 ratio to the intervention arm (N = 209) or the comparator arm (N = 206). Randomization in the C-POST study was stratified by anatomical region of the resected high-risk tumour (head and neck region vs. non-head and neck region), geographical region (North America vs. Australia/New Zealand vs. rest of the world), high-risk category (nodal vs. non-nodal), ECOG PS (0 vs. 1) and a history of CLL (present vs. absent).

The C-POST study comprises two phases: phase 1 of the study addresses the double-blind, direct comparison of cemiplimab versus placebo. Phase 2 of the study is unblinded and optional. In Phase 2, patients from Phase 1 with confirmed recurrence may receive 96-week treatment with cemiplimab, regardless of which arm they were assigned to in Phase 1. Patients who were randomized to the intervention arm in Phase 1 could only receive cemiplimab again in Phase 2 if the recurrence had occurred no earlier than 3 months after the completion of the 48-week treatment.

In Phase 1 of the study, cemiplimab was administered in accordance with the SmPC [8]. According to the original protocol, 350 mg of cemiplimab were administered every 3 weeks over a 48-week period. Under Protocol Amendment 2 of 29 June 2021, the dosing regimen was adjusted and 350 mg of cemiplimab were administered every 3 weeks over a 12-week period (4 doses of the study medication), followed by 700 mg of cemiplimab every 6 weeks for a further 36 weeks (6 doses). Both dosing regimens are in accordance with the SmPC [8]. Treatment was continued until the end of the planned 48-week treatment period, until

recurrence, unacceptable toxicity or withdrawal of consent. For the purposes of blinding, a placebo corresponding to the intervention was administered in the comparator arm. Treatment of AEs or immune-mediated AEs, including the administration of systemic corticosteroids, was permitted in both arms.

Primary outcome of the C-POST study was DFS. Secondary outcomes were overall survival and outcomes of the categories morbidity, health-related quality of life and side effects.

Uncertainties in the C-POST study

Risk classification for the high risk of recurrence

In accordance with the inclusion criteria, the following risk factors for a high risk of recurrence were identified:

- nodal disease with extracapsular extension and at least one lymph node > 20 mm in the pathological findings and/or ≥ 3 positive lymph nodes in the surgical pathology report
- ITM, defined as skin or subcutaneous metastases located > 2 cm from the primary cSCC tumour but not extending beyond the regional lymph node station
- T4 tumour, including head and neck tumour and non-head and neck tumour
- perineural invasion, defined as clinical and/or radiological involvement of the nerves
- recurrent cSCC, defined as cSCC occurring within the area of the previously resected tumour (with additional characteristics such as, for example, poorly differentiated histology or stage $\geq$ N2b disease)

According to the S3 guideline 'Actinic keratosis and squamous cell carcinoma of the skin', issued by the AWMF, there is generally no uniform classification system for identifying patients as having high-risk cSCC [9]. Overall, the following key risk factors can be identified, although it is unclear how the individual factors should be weighted:

- tumour diameter > 20 mm
- infiltration depth > level 3
- de-differentiation
- perineural invasion
- location: ear and lower lip
- immunosuppression
- histological tumour thickness > 6 mm
- desmoplasia

The risk factors selected by the company deviate from those set out in the S3 guideline. Furthermore, no information is available on certain characteristics, such as tumour thickness, either in the dossier or in the study documentation.

For this research question, all patients were required to have undergone prior surgery and adjuvant radiotherapy. According to the guidelines, adjuvant radiotherapy is not recommended as standard, but only in the presence of certain risk factors for recurrence. The S3 guideline recommends adjuvant radiotherapy for:

- R1 or R2 resection and the inability to perform a re-excision
- extensive lymph node involvement (> 1 affected lymph node, a lymph node metastasis > 3 cm or a breach of the capsule)
- intraparotid lymph node involvement
- extensive perineural sheath infiltration

The criteria selected by the company to characterize a high risk of recurrence therefore largely represent the factors for which adjuvant radiotherapy is recommended according to the guidelines. It can therefore be assumed that, despite the deviations from the factors for high-risk cSCC listed in the guideline, the patient population in the C-POST study adequately represents the patient population of this research question.

Presence of an R0 resection or complete radiological response

In accordance with its information on the ACT, the G-BA assumes that patients have undergone an R0 resection or have achieved a complete radiological response. In accordance with the inclusion criteria, the patients had undergone macroscopic surgery for a pathologically confirmed cSCC prior to the start of the study. The dossier does not provide any information on the number of patients who underwent an R0 resection or achieved complete radiological response at baseline. The EPAR contains data from a post-hoc analysis on the type of resection performed in patients with stage T3, T4, T4a and T4b tumour sizes [6]. 46.9% of all the randomized patients in the intervention arm and 45.1% in the comparator arm had one of these tumour stages. Around 46% of these patients in the intervention arm and around 49% in the comparator arm underwent an R0 resection. In relation to all randomized patients, it is known that only 21.5% in the intervention arm and 22.3% in the control arm underwent an R0 resection. Around 45% of patients in the intervention arm underwent an R1 resection, compared with around 41% in the comparator arm. It is also known that, in relation to the total population, 21.1% of patients in the intervention arm and 18.4% in the comparator arm underwent an R1 resection at tumour sizes $\geq$ T3. In approximately 9% of patients with tumour sizes $\geq$ T3, it was not possible to evaluate the result of the surgery. The EPAR also provides no data on radiological response.

This research question addresses a group of patients who have undergone both surgery and adjuvant radiotherapy. As described, adjuvant radiotherapy is only recommended where a combination of specific risk factors is present. An R1 resection is a factor for which adjuvant radiotherapy is recommended in accordance with the S3 guideline [9]. The fact that an R0 resection has not been performed does therefore not mean that the patients are not covered by this research question.

The guidelines do not include any recommendations for monitoring response following adjuvant radiotherapy that go beyond the superordinate follow-up recommendations. It can therefore be assumed that the success of adjuvant radiotherapy is reflected in the absence of at least early recurrence. Furthermore, due to various factors, an assessment of the radiological response is difficult immediately after radiation has been completed. For example, oedema and inflammatory processes can make imaging more difficult [10]. The S3 guideline does not contain any direct recommendation regarding the radiation dose for post-operative radiotherapy. However, there are references in the literature to post-operative radiation with a total dose of 50 to 60 Gy. Patients in the C-POST study had to receive a radiation dose of at least 50 Gy in accordance with the inclusion criteria. The majority of patients (76% in both treatment arms) received a radiation dose of 60 to 69 Gy.

Given that adjuvant radiotherapy is only carried out in the presence of certain risk factors, for example in patients who have undergone R1 resection, and given that the patients in the study were treated with an adequate dose of radiation, it is assumed that the study population is sufficiently representative of the research question, even though no specific details are available regarding the surgery and radiotherapy undertaken prior to enrolment in the study.

Permitted radiochemotherapy following surgery

In accordance with the inclusion criteria, concomitant chemoradiotherapy was permitted following surgery. Adjuvant chemoradiotherapy is not covered by the present research question. Information on how many patients received chemoradiotherapy this is not available. However, the study report does provide data on the proportion of patients who received systemic therapy for the treatment of cSCC prior to study inclusion. The proportions were comparable, at 3.3% in the intervention arm and 6.3% in the control arm, and were low overall. Consequently, the use of chemoradiotherapy as an adjuvant treatment has no consequences for the benefit assessment.

Implementation of watchful waiting in the study

The G-BA specified watchful waiting as the ACT. In the C-POST study presented by company, patients in the comparator arm were no longer actively treated for their high-risk cSCC following surgery and radiation, but were instead given a placebo corresponding to the

intervention. The aim in both treatment arms was to provide individually optimized and supportive treatment to alleviate symptoms.

The following examinations were performed for assessing the health status or detecting recurrences in the C-POST study:

- A full physical examination upon screening, during the study treatment at the start of Cycles 2 to 4, and at the end of the treatment phase. Additionally, limited physical examinations were carried out at shorter intervals. As part of the follow-up, a full physical examination is carried out every 4 months during the first and the second year, and every 6 months from the third year onwards.
- Imaging (CT or MRI) during the planned 48-week treatment period, upon screening and at the end of each 12-week cycle, as well as every 4 months during the first 2 years of the planned follow-up and subsequently every 6 months until recurrence, death or the end of the study. Additional earlier imaging is possible at the investigator's discretion.
- histological or cytological confirmation of recurrence by means of a biopsy (unless the investigator considers a biopsy to pose an unacceptable safety risk, e.g. in the case of brain lesions)

The investigations performed in the C-POST study largely reflect the recommendations set out in the guidelines [9,11,12]. The AWMF states that approx. 80% of recurrences occur within the first two years following the primary diagnosis and recommends close follow-up at three-month intervals during the first two years for patients at high risk of recurrence, followed by follow-up at three- to six-month intervals from the third to the fifth year, and thereafter, depending on the risk profile, follow-up at intervals ranging from 3 months to once a year, comprising a physical examination, lymph node sonography and imaging techniques (such as CT or MRI) if a recurrence is suspected [9].

Data cuts

In accordance with the study protocol, three further interim analyses were conducted following the amendment to the study protocol dated 29 June 2021 (Amendment 2) in addition to the originally planned final analysis at approximately 165 DFS events in the total population: after approximately 83 DFS events (50% of 165 DFS events), after around 107 (65%) and after around 132 DFS events (80%). The company presents analyses on 2 data cuts in Module 4 A of the dossier. The first data cut-off of 4 October 2024 represents the prespecified interim analysis of 50% of the DFS events in the total population. At the time of the data cut, 89 DFS events had occurred. The second data cut (the most recent data cut of 7 April 2025) is a non-prespecified data cut involving 97 DFS events (approx. 59%). The date of the second data cut coincides with the submission of the documents of marketing authorization procedure to the EMA on 7 April 2025 [6]. It can therefore be assumed that this

data cut was not requested by the EMA. The results of the first data cut were used for this benefit assessment.

However, not all the relevant analyses for the first data cut are included in full in the dossier. For example, there are no analyses at the SOC and PT levels for the outcome discontinuation due to AEs, nor are there any subgroup analyses for all characteristics for the outcome overall survival.

Planned duration of follow-up

Table 8 shows the planned duration of patient follow-up for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: cemiplimab versus placebo

Study outcome category outcome	Planned follow-up
C-POST	
Mortality	
Overall survival	Until death or study end
Morbidity	
Failure of the curative treatment approach ^a	Until recurrence, death or end of the study
Symptoms (EORTC QLQ-C30)	Until recurrence
Health status (EQ-5D VAS)	Until recurrence
Health-related quality of life	
EORTC QLQ-C30	Until recurrence
Side effects	
All outcomes in the side effects category	90 days after the end of treatment, or until the day before the first dose of cemiplimab in Phase 2, or until the start of another systemic therapy, whichever comes first
a. Presented based on the recurrence rate and disease-free survival, includes the events locoregional recurrence, distant metastases, and death without recurrence.	
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale	

The observation periods for the outcomes morbidity (symptoms and health status) and health-related quality of life are systematically shortened because they were only recorded until disease progression. The observation periods for the outcomes on side effects also are systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 90 days) or until the day before the first administration of cemiplimab in Phase 2 of the study. However, to draw a reliable conclusion on the total study

period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: cemiplimab vs. placebo

Study characteristic category	Cemiplimab N = 209	Placebo N = 206
C-POST		
Age [years], mean (SD)	69 (10)	69 (11)
Sex [F/M], %	17/83	16/84
Geographical region, n (%)		
North America	37 (18)	31 (15)
Australia/New Zealand	90 (43)	90 (44)
Rest of the world	82 (39)	85 (41)
Family origin, n (%)		
White	189 (90)	189 (92)
Asian	5 (2)	8 (4)
Other/unknown/not reported	15 (7) ^a	9 (4) ^a
ECOG PS, n (%)		
0	133 (64)	131 (64)
1	76 (36)	75 (36)
Location of the tumour, n (%)		
Head and neck	166 (79)	177 (86)
Not head or neck	43 (21)	29 (14)
Stage, n (%)		
I	2 (1)	5 (2)
II	3 (1)	4 (2)
III	53 (25)	52 (25)
IV	149 (71)	145 (70)
Unknown	2 (1)	0 (0)
High-risk category, n (%)		
Nodal	125 (60)	117 (57)
Non-nodal	84 (40)	89 (43)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: cemiplimab vs. placebo

Study characteristic category	Cemiplimab N = 209	Placebo N = 206
High-risk criterion, n (%)		
Lymph node involvement with ECE and ≥ 1 lymph node ≥ 20 mm	105 (50)	96 (47)
Lymph node involvement with ≥ 3 positive lymph nodes	33 (16)	37 (18)
In-transit metastases	20 (10)	21 (10)
T4 lesion	17 (8)	16 (8)
Perineural invasion	32 (15)	32 (16)
Recurrent cSCC + ≥ 1 additional factor ^b	55 (26)	50 (24)
$\geq$ N2b category in conjunction with the recurrent lesion	17 (31)	13 (26)
$\geq$ T3 category	37 (67)	29 (58)
Poorly differentiated histology and a diameter of ≥ 20 mm in the recurrent lesion	16 (29)	13 (26)
Time between completion of radiotherapy for high-risk cSCC and randomization [months], mean (SD)	1.4 (0.5)	1.4 (0.5)
Prior systemic cancer-related therapy, n (%)	7 (3)	13 (6)
Radiotherapy dosage, n (%)		
< 50 Gy	5 (2)	3 (2)
50–59 Gy	56 (27)	53 (26)
60–69 Gy	159 (76)	156 (76)
> 70 Gy	1 (< 1)	1 (< 1)
Treatment discontinuation, n (%) ^{c, d}	44 (21)	61 (30)
Study discontinuation, n (%) ^{c, e}	22 (11)	31 (15)
a. Institute's calculation. b. Patients with multiple risk factors are counted only once. c. Discontinuation for the randomized phase of the study (Phase 1) up to the data cut of 4 October 2024. d. Common reasons for treatment discontinuation in the intervention arm vs. the comparator arm were the following (percentages based on randomized patients): recurrence (5% vs. 24%), AEs (9% vs. 2%). In addition, 4 (2%) vs. 2 (1%) randomized patients never started treatment, and 60% vs. 53% of patients completed treatment as planned. e. A common reason for study discontinuation in the intervention vs. comparator arm (percentages refer to randomized patients) was withdrawal of consent (1% vs. 4%). The data additionally include patients who died during the course of the study (intervention arm: 6% vs. comparator arm: 6%). AE: adverse event; cSCC: cutaneous squamous cell carcinoma; ECE: extracapsular extension; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; Gy: Gray; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation		

The patient characteristics of the C-POST study are largely comparable between the two treatment arms. The mean age of the patients was 69 years and the majority were male (approximately 83 %). In both treatment arms, 64% of all patients had an ECOG PS of 0.

Before the start of the study, all patients underwent surgical removal of all visible tumours by means of a macroscopically complete resection of the cSCC. Around 70% of the resected tumours were at tumour stage IV. In addition, all patients received adjuvant radiotherapy. 76% of patients in both treatment arms were exposed to a total radiation dose of 60 to 69 Gy as part of their post-operative radiotherapy. The period between completion of the radiotherapy and randomization was 1.4 months (mean) in both treatment arms.

21% of the patients in the intervention arm versus 30% of the patients in the comparator arm discontinued treatment. Common reasons for treatment discontinuation were recurrences (5% in the intervention arm and 24% in the comparator arm) and side effects (9% in the intervention arm and 2% in the comparator arm). 11% in the intervention group and 15% in the comparator arm discontinued the study. In both treatment arms, the main reason for this was patient decision.

Information on the course of the study

Table 10 shows patients' mean and median treatment durations as well as the mean and median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: cemiplimab vs. placebo

Study duration of the study phase outcome category / outcome	Cemiplimab N = 205	Placebo N = 204
C-POST		
Treatment duration [months]		
Data cut 1		
Median [Q1; Q3]	11.0 [5.9; 11.0] ^a	11.0 [5.5; 11.0] ^a
Mean (SD)	8.6 (3.6) ^a	8.3 (3.5) ^a
Observation period [months] ^b		
Overall survival	ND	ND
Morbidity		
Recurrence	ND	ND
Symptoms (EORTC QLQ-C30)	ND	ND
Health status (EQ-5D VAS)	ND	ND
Health-related quality of life (EORTC QLQ-C30)	ND	ND
Side effects	ND	ND
a. Institute's calculation from data in weeks. b. Data are available only for the entire study observation duration: The median follow-up period for the entire study duration (including Phase 2) was 24.0 months (min: 2 months, max: 64 months) for the entire study population. The median follow-up period for the intervention group was 24.5 months (min: 2, max: 61 months); for the comparator group, it was 23.8 months (min: 2, max: 64 months). Up to the first data cut, patients in Phase 1 of the study were followed up for a median period [Q1; Q3] of 23.49 [10.25; 34.07] months in the intervention arm versus 13.24 [6.21; 28.85] months in the comparator arm. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale		

In Module 4A of the dossier, the company only provides information on the median treatment duration. This was 11 months in both treatment arms. This means that at least 50% of patients in both arms completed the treatment. Median follow-up durations for the individual outcomes are not available. The median total duration of follow-up in the study up to the first data cut (including Phase 2 of the study) was about 24.5 months in the intervention arm and about 23.8 months in the comparator arm. For Phase 1 of the study, the median follow-up periods up to the data cut were 23.5 months in the intervention arm compared to 13.2 months in the comparator arm. e. No information is available on how the observation periods were estimated. For this reason, there is uncertainty as to why the duration of follow-up in Phase 1 of the study differs significantly between the arms, and whether this is primarily connected to the time points of recurrence events and a related transition to Phase 2 of the study. As the

follow-up periods for the outcomes on side effects were linked to treatment with the study medication (plus 90 days), the follow-up periods for these outcomes are potentially shortened compared with those for overall survival; however, presumably they are sufficiently comparable between the treatment arms. The outcomes on symptoms and health-related quality of life were only recorded up to the point of recurrence and are therefore also shortened. Due to the lack of outcome-specific observation periods, it is not possible to assess whether the observation periods for these outcomes are comparable across the treatment arms.

A meaningful assessment of the curative treatment approach generally requires a sufficiently long follow-up period after the end of treatment, extending beyond the high-risk period. This is particularly due to the situation given in the intervention arm of the C-POST study and, in relation to the experimental intervention, means a sufficiently long follow-up after the end of the 48-month therapy with cemiplimab. This is intended to ensure that, once treatment is discontinued, relapses are actually prevented rather than merely delayed. Furthermore, it remains unclear how it was ensured that patients were tumour-free at baseline. This uncertainty would require an even longer follow-up period. The AWMF states that approx. 80 per cent of recurrences occur within the first two years following the primary diagnosis and recommends close follow-up at three-month intervals during the first two years, followed by a monitoring at three- to six-month intervals for year 3 to 5, and subsequently, depending on the risk profile, follow-up every 3 months to once a year [9]. The follow-up periods currently applied in this study therefore do not adequately cover the high-risk period for this therapeutic indication.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent systemic antineoplastic therapiesa – RCT, direct comparison: cemiplimab versus placebo

Study drug	Patients with subsequent therapy, n (%)	
	cemiplimab N = 209	placebo N = 206
C-POST		
Number of patients with recurrence ^b	18 (8.6)	61 (29.6)
Number of patients with a recurrence who received subsequent treatment ^c	13 (6.2)	54 (26.2)
Surgery	4 (30.8)	11 (20.4)
Radiation	5 (38.5)	7 (13.0)
Systemic treatment	10 (76.9)	51 (94.4)
Cemiplimab (Phase 2)	3 (23.1)	46 (85.2)
Cemiplimab (not in Phase 2)	2 (15.4) ^d	5 (9.3) ^e
Other systemic therapies	6 (46.2) ^f	6 (11.1)
5-FU	1 (7.7)	0 (0)
Carboplatin + paclitaxel	1 (7.7)	2 (3.7)
5-FU + cisplatin	1 (7.7)	1 (1.9)
Protein kinase inhibitor	1 (7.7)	0 (0)
Cetuximab, monotherapy	1 (7.7)	2 (3.7)
Cetuximab + paclitaxel	1 (7.7)	0 (0)
Cetuximab + docetaxel	1 (7.7)	0 (0)
Carboplatin + 5-FU + cetuximab	0 (0)	1 (1.9)
Carboplatin, monotherapy	0 (0)	1 (1.9)
Total number of other systemic therapies (not in Phase 2)	8 (61.5)	12 (22.2)
a. 1st subsequent therapy following a relapse. b. This does not include patients for whom the recurrence event was death from any cause. c. The following percentages are based on this population (Institute's calculation). d. Two patients received cemiplimab both in Phase 2 and as standard treatment outside Phase 2 and are not shown here. e. One patient received cemiplimab both in Phase 2 and as standard treatment outside Phase 2 and is not shown here. f. One patient received three lines of treatment (cetuximab + paclitaxel and two lines of cetuximab + docetaxel) and is counted once here. FU: fluorouracil; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial		

In its dossier, the company presents aggregated information on the type of the first subsequent therapies used in the C-POST study.

Although the choice of subsequent antineoplastic therapies was not restricted in both arms of the C-POST study, there was a tendency to favour cemiplimab as subsequent therapy due to the possibility of transition to Phase 2 of the study.

In the C-POST study, approximately 38.5% of the patients who received a first subsequent therapy were administered cemiplimab in the intervention arm. In the comparator arm, 94.5% of patients with subsequent therapy received cemiplimab as their first subsequent therapy. Based on patients with a recurrence in the comparator arm, this proportion amounts to 83.6%. Therefore, cemiplimab was the most commonly used subsequent therapy in the study. Cemiplimab is approved for the treatment of locally advanced or metastatic cSCC when curative surgery or curative radiation are unsuitable [8].

Related to patients with recurrence and subsequent therapy, approx. 39% in the intervention arm and 13% in the comparator arm received radiotherapy. Surgeries were performed in 31% of patients in the intervention arm and 20% of patients in the comparator arm.

Where possible, the tumour should be surgically removed in case of a local or locoregional recurrence according to the German S3 guideline. If complete resection is not possible, postsurgical radiation of the lesions remaining after R1 or R2 resection is recommended [9]. In patients with locally advanced or metastatic cSCC whose disease cannot be treated by surgery or radiation, the indication for systemic therapy should be assessed. It should be noted that, in accordance with the S3 guideline, there are currently no standardized criteria for defining locally advanced cSCC. The assessment of a patient's suitability for systemic therapy should, where possible, be carried out by an interdisciplinary tumour board [9]. Both the AWMF and the European Association of Dermato-Oncology (EADO) recommend that, where systemic therapy is the appropriate treatment, immunotherapy with a PD-1 inhibitor should be used in the first line [9,12]. If the disease progresses under PD-1 inhibition, epidermal growth factor receptor (EGFR)-targeted therapy or chemotherapy should be used.

In the C-POST study, 10 patients in the intervention arm and 26 patients in the comparator arm had a distant recurrence. Systemic therapy would therefore, in principle, be suitable for these patients. No information is available on which form of treatment was used in the subsequent therapy for which type of recurrence. However, significantly more patients received systemic therapy with cemiplimab. It can therefore be assumed that patients with a locoregional recurrence have also received systemic therapy. However, as described, there is no information available as to the criteria on which the decision for systemic therapy was based. Furthermore, there is no information available on how many patients had an isolated local recurrence. It is therefore not possible to assess how many patients were eligible for local treatment forms such as surgery and radiation.

There is uncertainty as to the proportion of patients for whom the decision for systemic therapy was made, and on the basis of which criteria. Based on the available information, it cannot be determined whether it could be safely ruled out that all patients who received subsequent therapy with cemiplimab could have undergone further surgery or radiation. Furthermore, there are uncertainties as to whether re-treatment with cemiplimab is appropriate for patients in the intervention arm following the onset of a recurrence, and whether the period of at least 3 months after completion of adjuvant cemiplimab therapy is sufficient to use cemiplimab again in the relapse therapy. The majority of patients in the intervention arm received chemotherapy or a cetuximab-containing therapy. Treatment with cetuximab corresponds to the recommendations of the guideline after progression under a previous therapy with an immune checkpoint inhibitor [9].

Whilst overall the subsequent therapies used in the C-POST study are therefore in line with the systemic treatments recommended by the S3 guideline for locally advanced or metastatic disease, it remains unclear to what extent a systemic therapy was suitable for all patients, and on the basis of which criteria this suitability was determined. It is therefore also unclear what consequences this will have for the interpretability of the outcome overall survival. As this assessment provides no data for the benefit assessment (see Section I 4.3), this uncertainty has no consequences for the benefit assessment at this point in time.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: cemiplimab vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
C-POST	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the C-POST study.

Transferability of the study results to the German health care context

The company considers the results of the C-POST study to be transferable to the German health care context. The company does not provide any specific justification for the transferability of the results of the C-POST study to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
 - overall survival
- Morbidity
 - failure of the curative treatment approach (represented via DFS)
 - symptoms
 - recorded using the EORTC QLQ-C30
 - health status
 - recorded using the EQ-5D VAS
- Health-related quality of life
 - recorded using the EORTC QLQ-C30
- Side effects
 - serious AEs (SAEs)
 - severe AEs (CTCAE grade ≥ 3)
 - discontinuation due to AEs
 - immune-mediated SAEs
 - immune-related severe AEs (CTCAE grade ≥ 3)
 - other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4).

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: cemiplimab versus placebo

Study	Outcomes										
	Overall survival	Failure of the curative treatment approach ^a	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs ^b	Discontinuation due to AEs	Immune-mediated SAEs	Immune-mediated severe AEs	Hypothyroidism (PT, AEs)
C-POST ^c	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
a. Operationalized as recurrence rate and disease-free survival , includes the events local recurrence, regional recurrence, distant metastases, and death from any cause. b. Severe AEs are operationalized as CTCAE grade ≥ 3. c. No suitable data available; see Section I 4.3 for the reasoning. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale											

Notes on outcomes

Failure of the curative treatment approach

Failure of the curative treatment approach was therefore considered a patient-relevant event in this assessment. Failure of the curative treatment approach was therefore considered a patient-relevant outcome in this assessment.

In the C-POST study, failure of the curative treatment approach was not directly recorded as an outcome. As an approximation, the present assessment considers the events that were recorded as part of the primary outcome of the C-POST study, i.e. the composite outcome of DFS, as operationalization for the outcome. The proportion of patients with event (referred to below as event rate) and also the time to the occurrence of an event (DFS) is relevant to the assessment. The operationalization of the outcome is explained below.

According to the dossier, DFS was defined as the time from randomization to the first documented recurrence of the disease (local, regional and/or distant, or death from any cause):

- Locoregional recurrence at one of the following sites:
 - head and neck cSCC: recurrence in the soft tissues of the neck or the cervical lymph nodes

- non-head-and-neck cSCC: recurrence in the first regional lymph node adjacent to the resected tumour (or in the soft tissue associated with the first adjacent lymph node basin)
- ITM, defined as skin or subcutaneous metastases located > 2 cm from the resected primary tumour but not outside of the regional lymph node station
- Distant recurrence at one of the following sites:
 - in head and neck cSCC: nodal recurrence below the clavicle
 - in non-head and neck cSCC: recurrence extending beyond the first adjacent lymph node basin of the resected tumour bed. A recurrence in two lymph node basins is regarded as a distant recurrence, even if they are adjacent (i.e. two mediastinal lymph node basins, two lymph nodes in the pelvic region).
 - recurrence in non-nodal tissue (including, but not limited to, the lungs, liver, bones and brain)
 - epidermotropic metastases (EDM), defined as distant lesion(s) in the dermis without involvement of the epidermis

The company specifies that new cSCC lesions should not be recorded as a recurrence event, as these lesions, which occur independently, are tumours that occur within the framework of a field cancerization. The emergence of a new primary tumour means that patients are not disease-free. In order to assess whether patients have been cured as a result of the treatment, it is therefore necessary to take these events into account when interpreting the outcome failure of the curative treatment approach and to present at least sensitivity analyses that take these events into account for both the DFS and the recurrence rate.

A DFS event was recorded in the C-POST study based on the decision of the investigator. Any suspected recurrence identified on imaging was confirmed by a subsequent biopsy (with the exception of cases where a biopsy would have posed an unacceptable safety risk).

In its dossier, the company does not provide any data on the event rates of the individual qualifying events. However, these can be found in the clinical study report (CSR).

As already described in Section I 3.2, the follow-up duration does not adequately cover the high-risk period for recurrence following the completion of treatment with cemiplimab. Thus, there are no suitable data available to carry out an overall assessment of the positive and negative effects across all outcome categories in the current situation. This is explained in Section I 4.3, taking into account the present data situation.

Patient-reported outcomes on symptoms, health status and health-related quality of life

Operationalization of the instruments EORTC QLQ-C30 and EQ-5D VAS

In its dossier, the company presents predefined analyses on responder analyses for the time to first clinically relevant deterioration and for the time to confirmed clinically relevant deterioration by 10 points (EORTC QLQ-C30) and by 7 points (EQ-5D VAS) for the outcomes morbidity and health-related quality of life. In addition, post-hoc analyses with a response threshold of 15 points for the EQ-5D VAS are available. It should be noted that, according to the PRO-SAP, not all scales of the EORTC QLQ-C30 should be included in the time-to-event analyses, but only those known as key scales. In the dossier, the company provided post-hoc time-to-event analyses for all scales.

In addition, there are predefined analyses on the change from baseline, as well as information on proportions of patients at each documentation date who have improved or deteriorated by 10 points (EORTC QLQ-C30) or 7 points (EQ-5D VAS), respectively.

With regard to the patient-reported outcomes recorded with the EORTC-QLQ-C30 and the EQ-5D VAS, analyses for the time to confirmed deterioration were also prespecified in addition to the analyses for the time to first clinically relevant deterioration. In this context, a confirmed deterioration was operationalized as the time to the first deterioration, which was subsequently confirmed by a deterioration in the subsequent recording. Missing values in the subsequent recording following a first deterioration were also counted as a confirmation. In principle, a confirmed deterioration is relevant in terms of content, as it reflects a more sustainable change than a one-off deterioration. However, as described, information on the outcome-specific follow-up periods is lacking. Based on the available information, it is therefore not possible to assess with sufficient certainty whether the data on confirmed deterioration are suitable in the present situation and operationalization. For this reason, the analyses on the time to first clinically relevant deterioration are presented in this benefit assessment.

Side effects

Recording of the progression of the underlying disease

According to the study protocol, events in the C-POST study that were clearly attributable to the progression of the underlying disease were not to be documented as an AE by the investigator. However, the available information on the documented AEs provides evidence that AEs attributable to the progression of the underlying disease are included in the analyses (see I Appendix C of the full dossier assessment). This applies in particular to the AE squamous cell carcinoma of the skin. Analyses would be required that do not include events relating to the progression of the underlying disease. For the results presented in Section I 4.3, it must be noted that these may be due to a combination of side effects and symptoms or late complications of the disease.

Immune-mediated SAEs and immune-mediated severe AEs

For PD-1 inhibitors such as cemiplimab, immune-mediated AEs represent a relevant outcome within the side effects category. The company does not provide any data on immune-mediated AEs in Module 4A. However, the study report presents the related information. In the C-POST study, severe immune-mediated AEs (CTCAE grade ≥ 3) were identified as AEs of special interest (AESI) using a prespecified list with preferred terms (PT) that are potentially immune-mediated. This PT list sufficiently covers potential immune-mediated AEs. According to the study documentation, the immune-mediated AEs identified in this way constitute the potential immune-mediated AEs. Every immune-mediated AE that had been treated with systemic corticosteroids and/or immunosuppressants, or that had been classified as an immune-mediated endocrinopathy, was then designated as an identified immune-mediated AE. It is not appropriate to link immune-mediated AEs to a treatment. This benefit assessment therefore presents the results of the potential immune-mediated AEs (see I Appendix C of the full dossier assessment).

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: cemiplimab versus placebo

Study	Study level	Outcomes										
		Overall survival	Failure of the curative treatment approach ^a	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs ^b	Discontinuation due to AEs	Immune-mediated SAEs	Immune-mediated severe AEs	Hypothyroidism (PT, AEs)
C-POST ^c	L	L	L	H ^d	H ^d	H ^d	H ^e	H ^e	L ^f	H ^e	H ^e	H ^e

a. Operationalized as recurrence rate and disease-free survival, includes the events local recurrence, regional recurrence, distant metastases, and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3 .
c. No suitable data available; see Section I 4.3 for the reasoning.
d. Incomplete observations for potentially informative reasons, where follow-up observations are likely to vary and the response rate to questionnaires declines over the course of the study.
e. Incomplete observations for potentially informative reasons.
f. Despite a low risk of bias, the certainty of results for the outcome discontinuation due to AEs was assumed to be limited (see Sections I 4.3).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias is rated as low for the outcomes overall survival and failure of the curative treatment.

There is a high risk of bias for the outcomes on symptoms and health-related quality of life (each recorded with the EORTC QLQ-C30) and on health status (recorded with the EQ-5D VAS). This is due to incomplete observations for potentially informative reasons, as these outcomes were only followed up until the occurrence of a recurrence. This is likely to result in different follow-up periods between the arms, as the proportion of patients who discontinued treatment due to recurrence differs significantly between the arms. No information on the outcome-specific observation periods was available. Furthermore, a decline in the number of questionnaire responses has been observed over the course of the study. It is unclear to what extent this is due to administrative censoring at this timepoint.

Due to incomplete observations for potentially informative reasons, the risk of bias is rated as high for the outcomes SAEs, severe AEs, immune-mediated SAEs, immune-mediated severe AEs and hypothyroidism (PT, AEs).

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

I 4.3 Results

There are no suitable data available to assess the added benefit of cemiplimab compared with the ACT in adult patients with cSCC at high risk of recurrence after surgery and radiation. There is no hint of an added benefit of cemiplimab in comparison with the ACT; an added benefit is therefore not proven. However, the results are presented below as supplementary information.

Table 15 and Table 16 summarize the results on the comparison of cemiplimab with placebo in patients with cSCC at high risk of recurrence after surgery and radiation. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: cemiplimab versus placebo (multipage table)

Study outcome category	Cemiplimab		Placebo		Cemiplimab versus placebo
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	
C-POST					
Mortality					
Overall survival	209	NA 12 (5.7)	206	NA 13 (6.3)	0.86 [0.39; 1.90]; 0.715
Morbidity					
Failure of the curative treatment approach ^b					
Event rate ^c	209	24 (11.5)	206	65 (31.6)	RR: 0.35 [0.23; 0.54]; < 0.001 ^d
Locoregional recurrences	209	8 (3.8)	206	35 (17.0)	–
Distant recurrence ^e	209	10 (4.8)	206	26 (12.6)	–
Death	209	6 (2.9)	206	4 (1.9)	–
Disease-free survival	209	NA 24 (11.5)	206	49.4 [48.5; NC] 65 (31.6)	0.32 [0.20; 0.51]; < 0.001 ^a
Symptoms (EORTC QLQ-C30 – time to first deterioration ^f)					
Fatigue	ND ^g	5.62 [5.55; 8.34] 126 (60.3)	ND ^g	8.31 [5.65; 8.41] 102 (49.5)	1.10 [0.84; 1.43]; 0.478
Nausea and vomiting	ND ^g	NA [40.31; NC] 53 (25.4)	ND ^g	45.83 [30.75; NC] 48 (23.3)	0.85 [0.57; 1.26]; 0.422
Pain	ND ^g	10.64 [8.34; 14.09] 108 (51.7)	ND ^g	12.12 [8.38; 23.49] 92 (44.7)	1.19 [0.90; 1.58]; 0.221
Dyspnoea	ND ^g	23.52 [17.77; 30.98] 78 (37.3)	ND ^g	28.55 [17.97; NC] 61 (29.6)	1.07 [0.76; 1.51]; 0.687
Insomnia	ND ^g	14.23 [8.44; 31.38] 87 (41.6)	ND ^g	23.26 [14.59; NC] 68 (33.0)	1.15 [0.83; 1.59]; 0.387
Appetite loss	ND ^g	37.06 [22.51; NC] 62 (29.7)	ND ^g	NA [45.83; NC] 46 (22.3)	1.15 [0.79; 1.69]; 0.463
Constipation	ND ^g	43.96 [23.46; NC] 64 (30.6)	ND ^g	30.65 [21.82; NC] 60 (29.1)	0.87 [0.61; 1.25]; 0.460
Diarrhoea	ND ^g	NA [27.07; NC] 54 (25.8)	ND ^g	NA [28.81; NC] 48 (23.3)	0.92 [0.62; 1.36]; 0.678
Health status (EQ-5D VAS – time to first deterioration ^h)	ND ^g	28.85 [17.87; NC] 71 (34.0)	ND ^g	NA [22.21; NC] 57 (27.7)	1.19 [0.84; 1.69]; 0.326

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: cemiplimab versus placebo (multipage table)

Study outcome category outcome	Cemiplimab		Placebo		Cemiplimab versus placebo
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value ^a
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration ⁱ					
General health status/quality of life	ND ^g	13.83 [8.48; 25.30] 97 (46.4)	ND ^g	18.60 [8.41; 45.83] 80 (38.8)	1.09 [0.81; 1.47]; 0.575
Physical functioning	ND ^g	21.68 [16.39; 39.82] 79 (37.8)	ND ^g	18.46 [13.44; NC] 69 (33.5)	0.94 [0.68; 1.31]; 0.729
Role functioning	ND ^g	10.84 [8.38; 14.23] 105 (50.2)	ND ^g	11.33 [8.41; 25.69] 83 (40.3)	1.10 [0.82; 1.47]; 0.542
Emotional functioning	ND ^g	25.63 [14.23; NC] 77 (36.8)	ND ^g	22.21 [11.43; NC] 71 (34.5)	0.95 [0.69; 1.32]; 0.766
Cognitive functioning	ND ^g	13.90 [10.32; 22.47] 95 (45.5)	ND ^g	13.50 [9.33; 21.68] 84 (40.8)	0.91 [0.67; 1.22]; 0.539
Social functioning	ND ^g	14.32 [10.48; 25.13] 93 (44.5)	ND ^g	13.73 [8.41; 25.86] 79 (38.3)	0.98 [0.72; 1.33]; 0.898
a. HR and CI from Cox proportional hazards model, p-value from log-rank test, each stratified by high-risk tumour (HN vs. non-HN) and geographical region (North America vs. Australia/New Zealand vs. rest of the world)^h. b. Newly diagnosed primary tumours were not taken into account in the operationalization (see I 4.1). c. Proportion of patients, individual components are presented in the lines below. d. Logistic regression model, stratified by high-risk tumour (HN vs. non-HN) and geographical region (North America vs. Australia/New Zealand vs. the rest of the world). e. Number of qualifying events for the outcome DFS. b. Patients with multiple recurrences are counted only once. 6 patients had both locoregional and distant recurrences (1 in the intervention arm and 5 in the control arm) and are shown only under 'distant recurrences'. f. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). g. According to the company, all randomized patients were included in the analysis. At the same time, it can be seen in the PRO-SAP that patients with no baseline value or no value in the course of the study were censored on Day 1. For example, depending on the scale used, baseline data were missing for 8% to 11% of patients. Thus, no times of these patients were actually included in the analysis. The exact number of these patients cannot be calculated. h. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). i. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).					
CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; HN: head and neck; HR: hazard ratio; n: number of patients with an event; N: number of patients analysed; NC: not calculable; ND: no data; PRO-SAP: statistical analysis plan for patient-reported outcomes; RCT: randomized controlled trial; RR: relative risk; VAS: visual analogue scale					

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: cemiplimab versus placebo (multipage table)

Study outcome category	Cemiplimab		Placebo		Cemiplimab versus placebo
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	

Table 16: Results (side effects) – RCT, direct comparison: cemiplimab versus placebo

Study outcome category outcome	Cemiplimab		Placebo		Cemiplimab versus placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value ^a
C-POST					
Side effects					
AEs (supplementary information)	205	187 (91.2)	204	182 (89.2)	—
SAEs	205	36 (17.6)	204	19 (9.3)	1.84 [1.09; 3.11]; 0.022
Severe AEs ^b	205	49 (23.9)	204	29 (14.2)	1.62 [1.07; 2.46]; 0.024
Discontinuation due to AEs	205	20 (9.8)	204	3 (1.5)	6.63 [1.99; 22.10]; 0.002
Immune-mediated SAEs	205	19 (9.3)	204	1 (0.5)	18.91 [2.55; 139.92]; < 0.001 ^c
Immune-mediated severe AEs ^b	205	11 (5.4)	204	1 (0.5)	10.95 [1.43; 84.01]; 0.004 ^c
Hypothyroidism (PT, AEs)	205	24 (11.7)	204	6 (2.9)	3.90 [1.62; 9.39]; 0.002
a. Unless otherwise labelled, logistic regression model, stratified by high-risk tumour (HN vs. non-HN) and geographical region (North America vs. Australia/New Zealand vs. rest of the world).					
b. Operationalized as CTCAE grade ≥ 3.					
c. Institute’s calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [13]).					
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HN: head and neck; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event					

For the outcome failure of the curative treatment approach, there is a statistically significant difference in favour of the intervention, both in the time to event (effect measure: HR) and in the event rate (effect measure: RR). No statistically significant difference between the treatment arms was shown for the outcomes on symptoms, health-related quality of life and

overall survival. The outcomes in the side effects category show statistically significant differences to the disadvantage of the intervention.

No suitable data available for the benefit assessment due to the observation period being too short

As already described in Section I 3.2, the follow-up duration does not adequately cover the high-risk period for recurrence following the completion of treatment with cemiplimab. Thus, based on the results of the first data cut, there are no suitable data available to carry out an overall assessment of the positive and negative effects across all outcome categories in the current situation. This will be explained below, taking into account the present data situation.

In this therapeutic indication, curative therapy is generally possible and the aim of treatment. Recurrence following tumour resection and subsequent radiation means that the curative treatment approach has failed.

In order to meaningfully assess the failure of the curative treatment approach, it is generally necessary to carry out a sufficiently long follow-up period. This should, on the one hand, cover the high-risk period and, on the other hand, extend for a sufficiently long time beyond the end of treatment. This is intended to ensure that, once treatment is discontinued, relapses are actually prevented rather than merely delayed. According to the S3 guideline, most relapses in this therapeutic indication occur within the first two years after the primary diagnosis; intensified follow-up is therefore recommended during this period [9].

Information on the follow-up durations for patients in the C-POST study who had not experienced a DFS event by the date of the data cut is not available, but can be roughly classified based on the following data: The maximum follow-up durations for the first randomized person was approximately 64 months. The minimum possible follow-up duration for the last randomized person was approximately 2 months. The median follow-up period for the entire study duration was 24 months, however, this means that 50% of patients were followed up for a shorter period. Overall, based on the available data, it is assumed that the follow-up period after the end of the maximum 48-week adjuvant therapy with cemiplimab is not sufficiently long for a relevant proportion of patients without DFS event to reliably rule out recurrences following the discontinuation of treatment. This assessment is also supported by the fact that the Kaplan-Meier curve of the intervention arm does not yet appear to have reached a stable plateau in terms of DFS (see I Appendix B). Even after the end of treatment with cemiplimab, a relevant extent of events continue to occur. The Kaplan-Meier curves (see I Appendix B) also show that a large proportion of patients were already censored at an early time point. Before the background of the follow-up periods listed above, it can be assumed that these were predominantly cases of administrative censoring. Due to the large number of early censorings, the data could be interpreted meaningfully.

Failure of the curative treatment approach is the essential treatment goal in this therapeutic indication. As it is not possible to draw reliable conclusions for this outcome at the time of the first data cut, a sufficient overall assessment of the positive and negative effects across all outcome categories cannot be performed.

The EPAR indicates that, as part of its scientific advice, the EMA has recommended using a fixed follow-up period for the data analysis rather than an event-driven follow-up period in this therapeutic indication [6]. The company was advised to choose an analysis period for which the risk of recurrence in both arms is considered to be low. The EMA proposed a period of three years for this. This constitutes a sensible study design in the present situation. However, the company did not follow this proposal. As described in Section I 3.2, only the primary analysis on DFS after 161 DFS events was originally planned. A total of three new interim analyses were added with Protocol Amendment 2. With 89 DFS events that occurred, the data cut used comprises around 50% of the originally planned number of events for the primary analysis. The EMA comments on the data submitted by the company pertaining to the recurrences in the two data cuts performed to date, noting that, given the duration of the observation period, there is still uncertainty as to whether the occurrence of recurrences is being prevented or merely delayed. For this reason, the EMA recommends that further descriptive data on DFS be submitted, as well as the final analysis on overall survival after the marketing authorization.

In summary, the data are currently unsuitable to allow for an overall assessment of the positive and negative effects of cemiplimab compared with the ACT across all outcome categories.

For this reason, subgroup analyses will not be presented below.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of cemiplimab in comparison with the ACT is summarized in Table 17.

Table 17: Cemiplimab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with cutaneous squamous cell carcinoma at high risk of recurrence after surgery and radiation; adjuvant treatment ^b	Watchful waiting	Added benefit not proven ^c
a. Presented is the ACT specified by the G-BA. b. It is assumed that patients have undergone an R0 resection or have achieved a complete radiological response. c. Only patients with an ECOG PS of 0 or 1 were included in the C-POST study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS $\geq$ 2. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that by the company, which derived an indication of a major added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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I Appendix A Kaplan-Meier curves

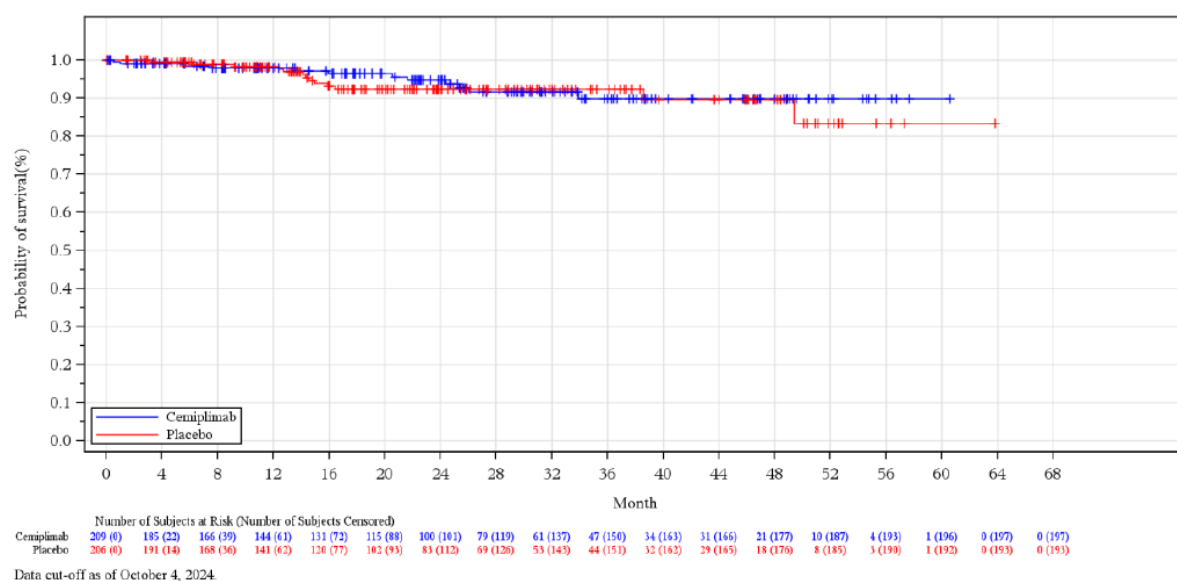


Figure 1: Kaplan-Meier curve on the outcome overall survival

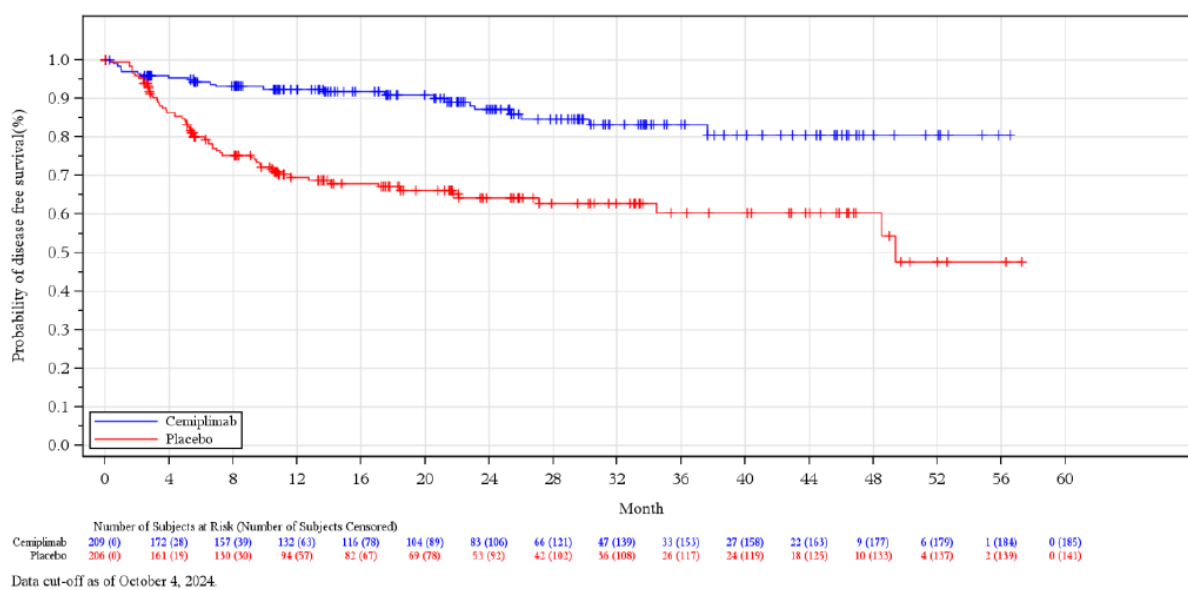


Figure 2: Kaplan-Meier curves on the outcome DFS

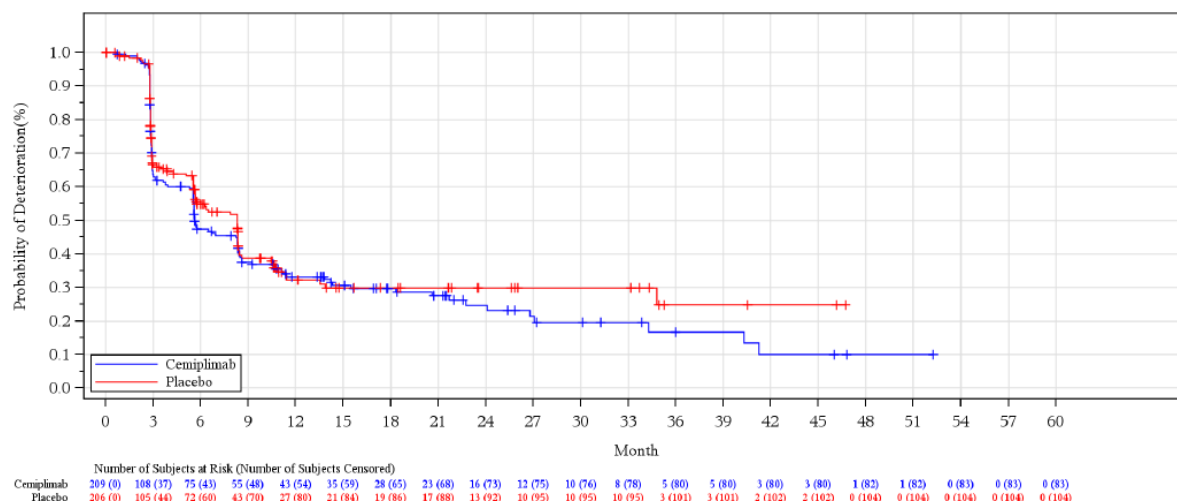


Figure 3: Kaplan-Meier curves on the outcome fatigue (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

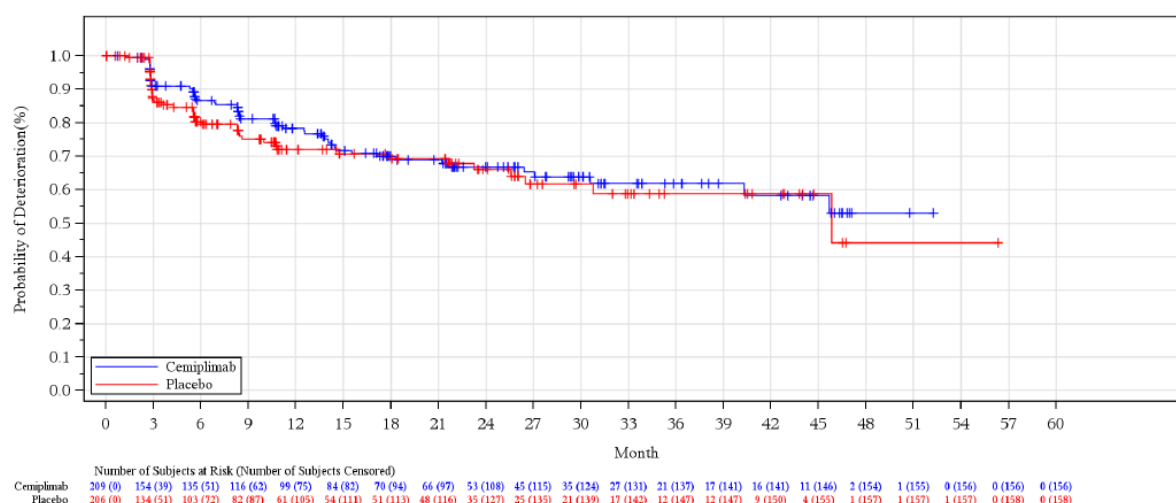


Figure 4: Kaplan-Meier curves on the outcome nausea and vomiting (EORTC QLQ-C30, first deterioration by ≥ 10 points)

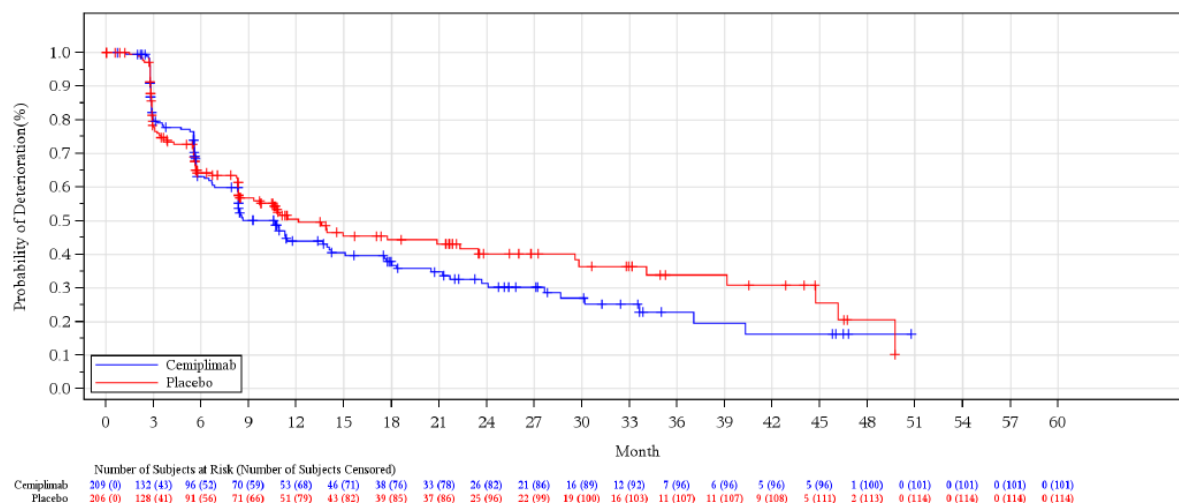


Figure 5: Kaplan-Meier curves on the outcome pain (EORTC QLQ C30, time to first deterioration by ≥ 10 points)

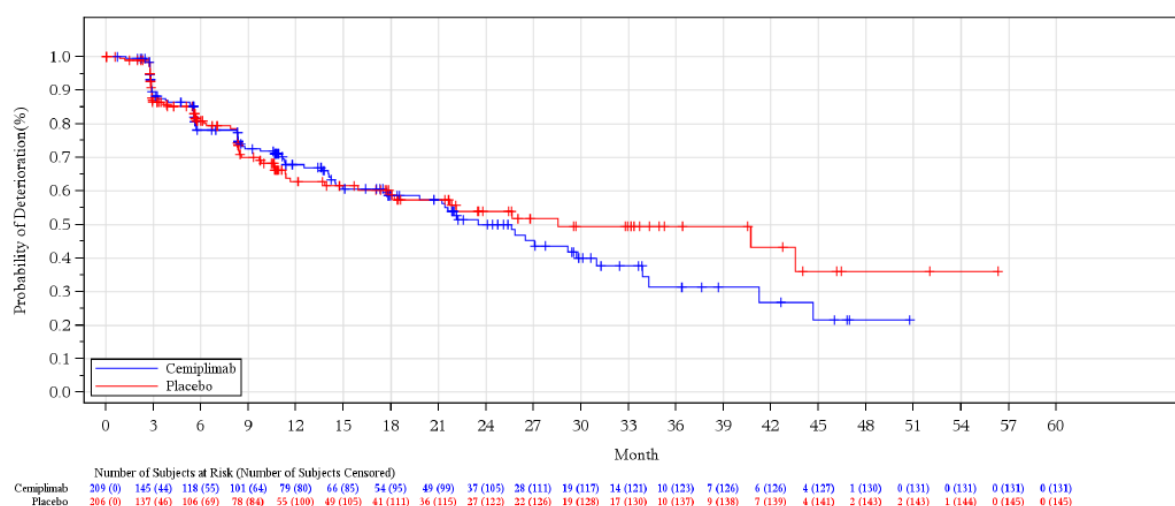


Figure 6: Kaplan-Meier curves on the outcome dyspnoea (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

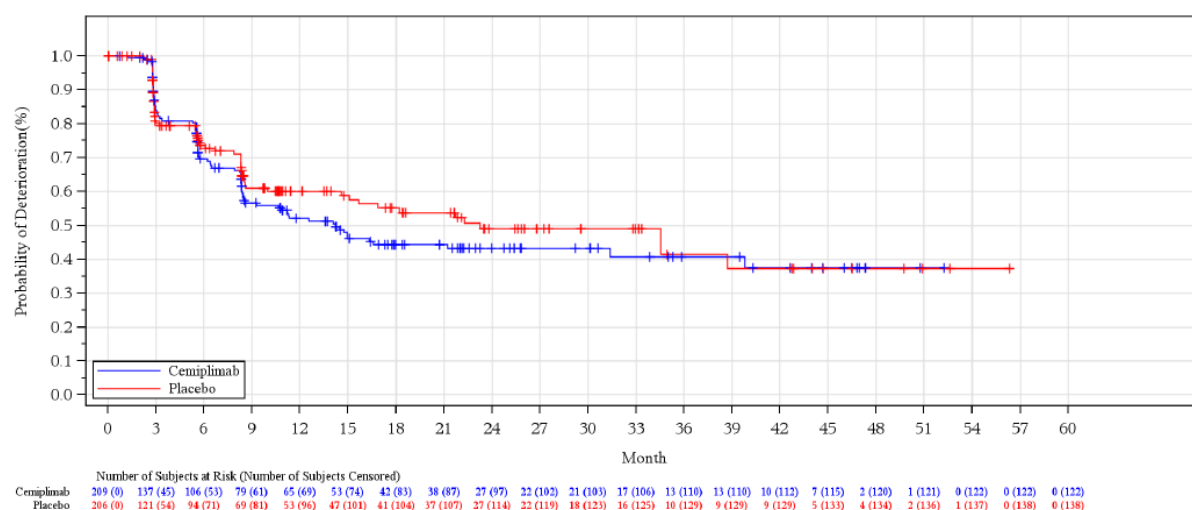


Figure 7: Kaplan-Meier curves on the outcome insomnia (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

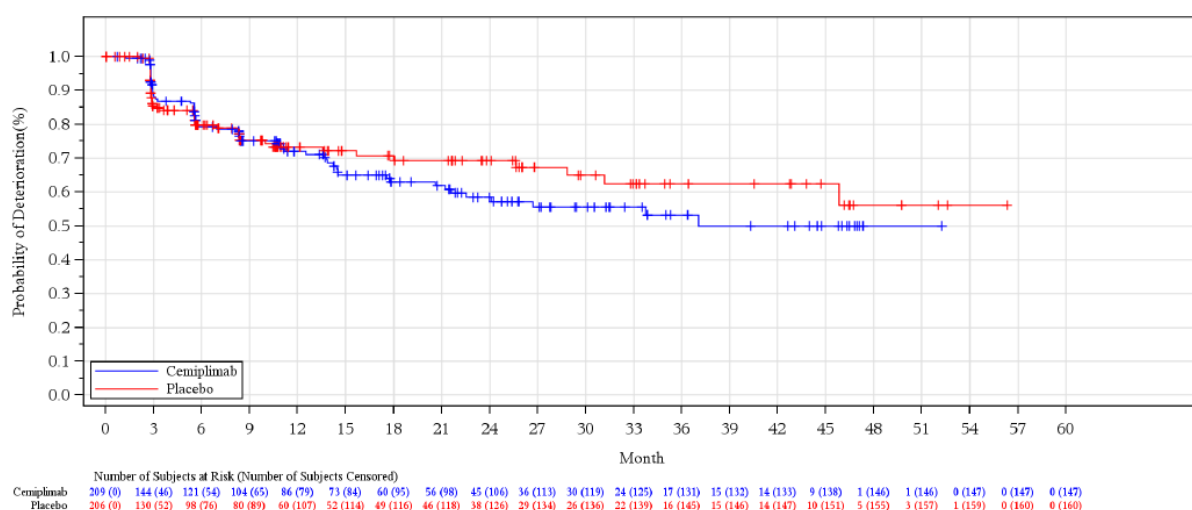


Figure 8: Kaplan-Meier curves on the outcome appetite loss (EORTC QLQ C30, time to first deterioration by ≥ 10 points)

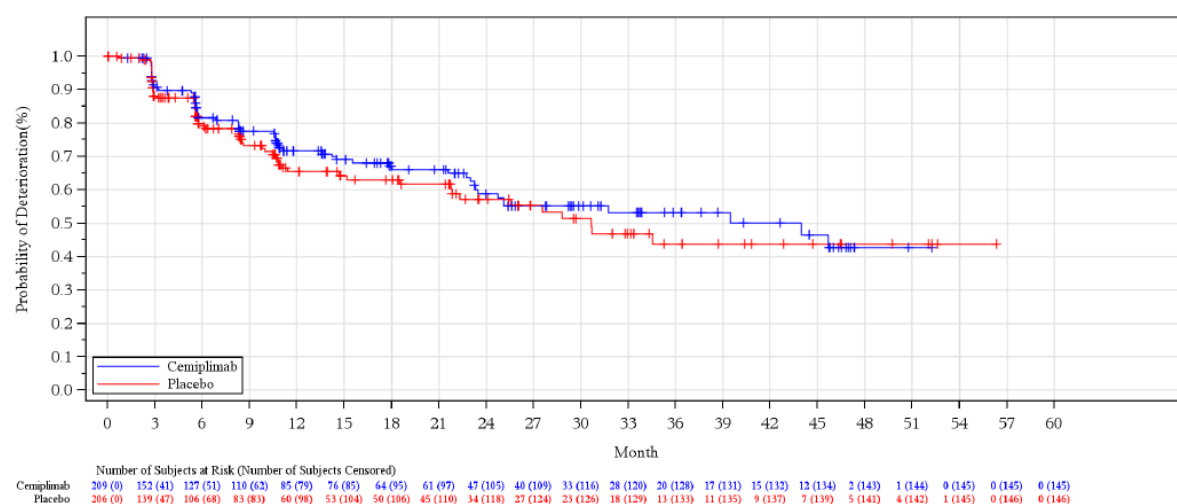


Figure 9: Kaplan-Meier curves on the outcome constipation (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

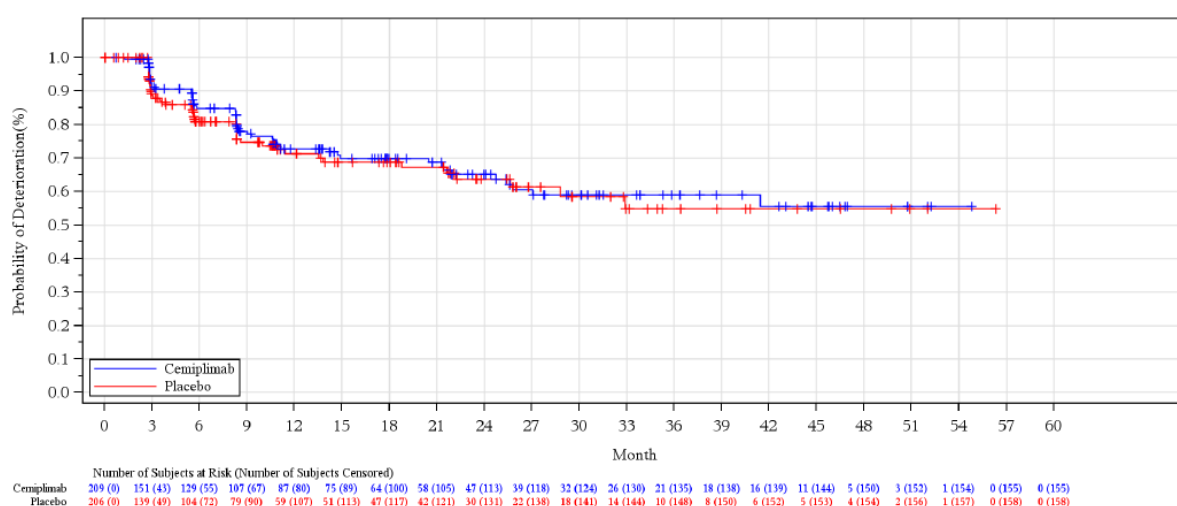


Figure 10: Kaplan-Meier curves on the outcome diarrhoea (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

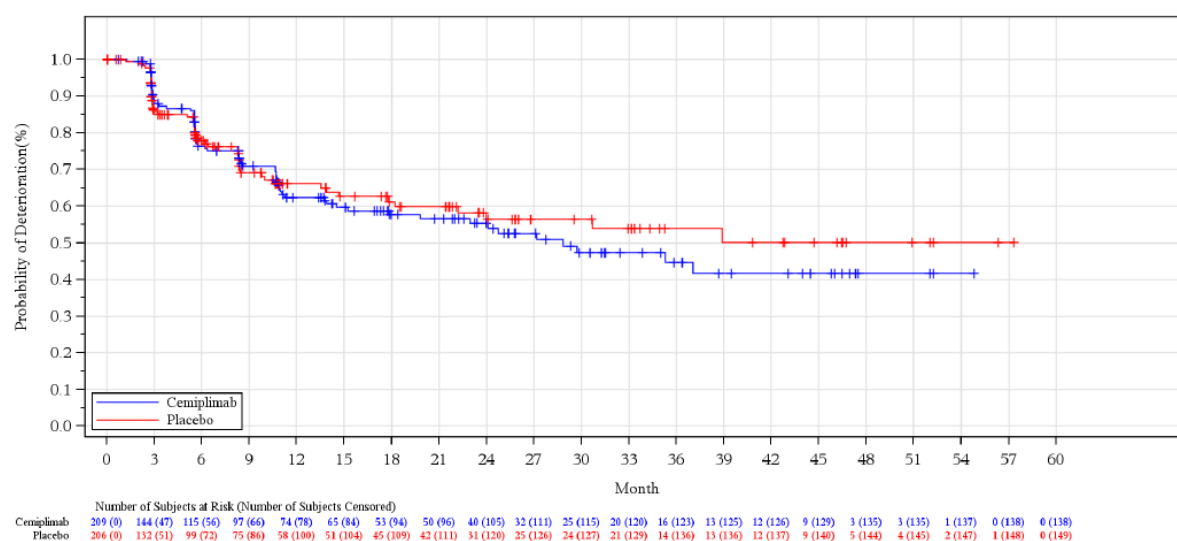


Figure 11: Kaplan-Meier curves on the outcome health status (EQ-5D VAS, time to first deterioration by ≥ 15 points)

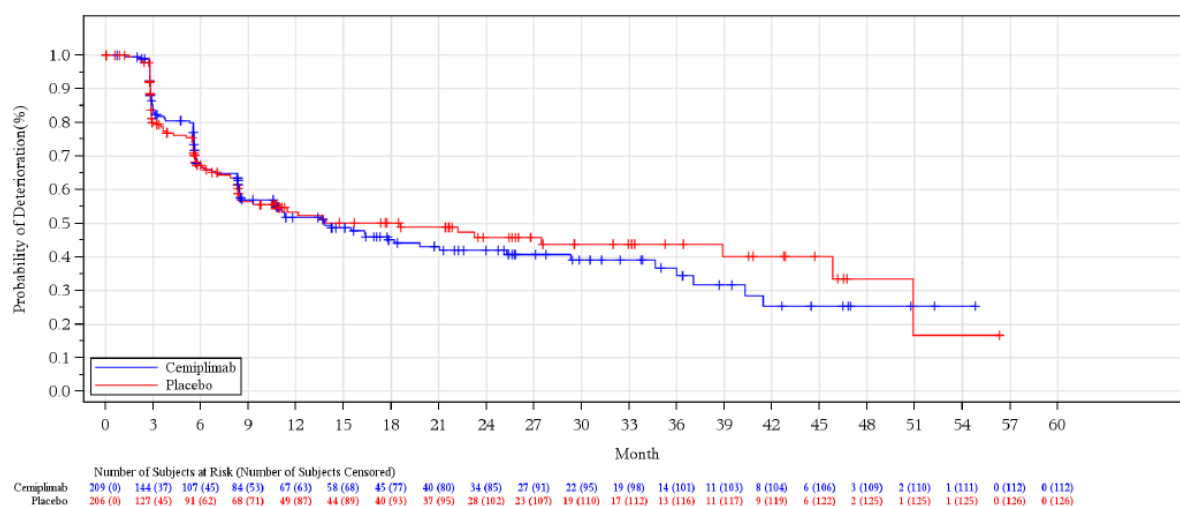


Figure 12: Kaplan-Meier curves on the outcome general health status/quality of life (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

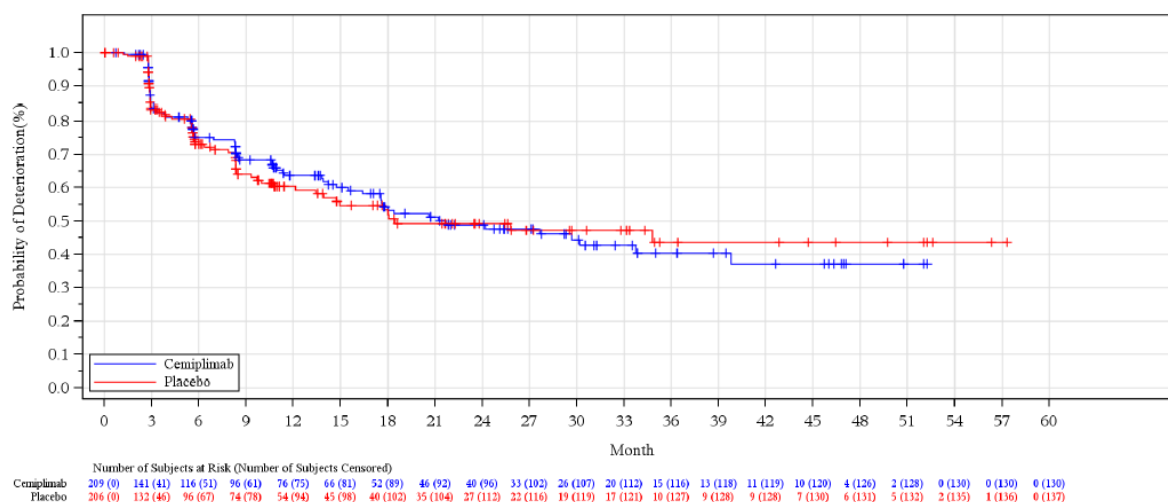


Figure 13: Kaplan-Meier curves on the outcome physical functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

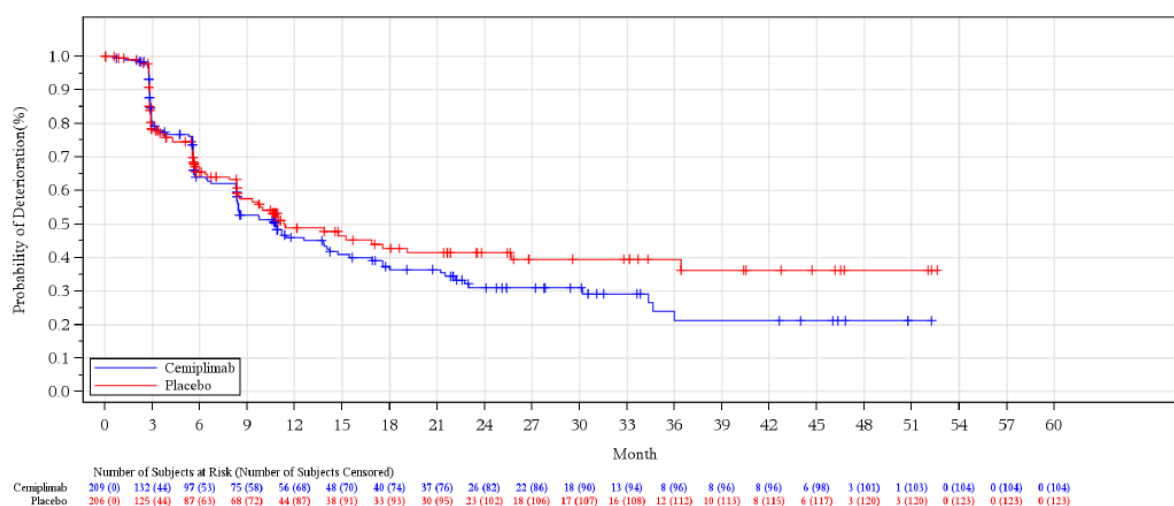


Figure 14: Kaplan-Meier curves on the outcome role functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

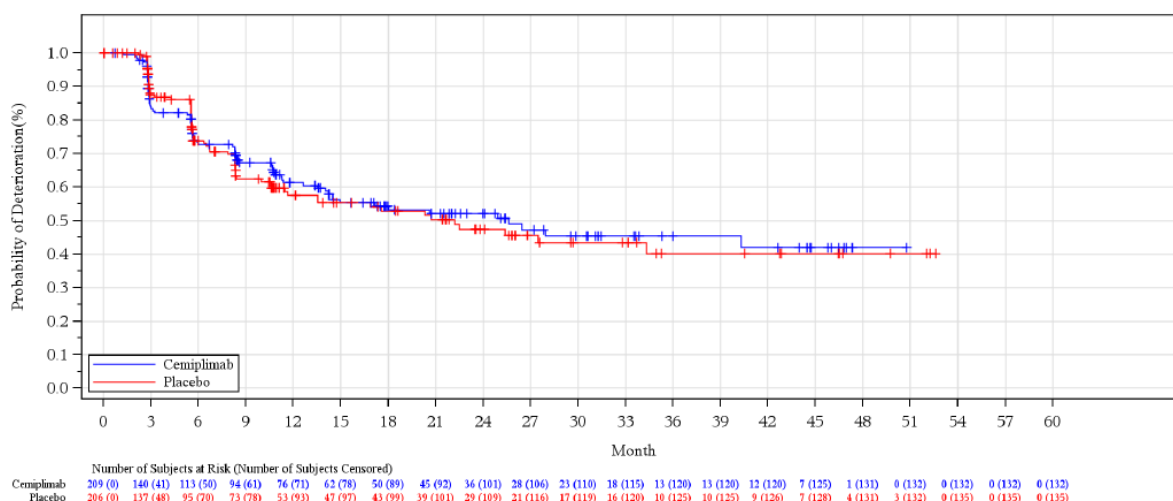


Figure 15: Kaplan-Meier curves on the outcome emotional functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

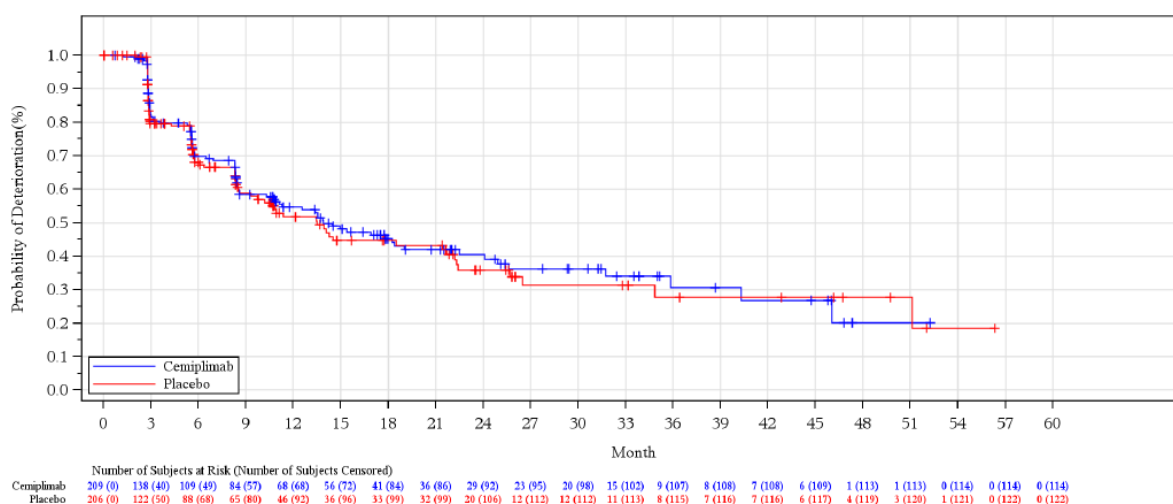


Figure 16: Kaplan-Meier curves on the outcome cognitive functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

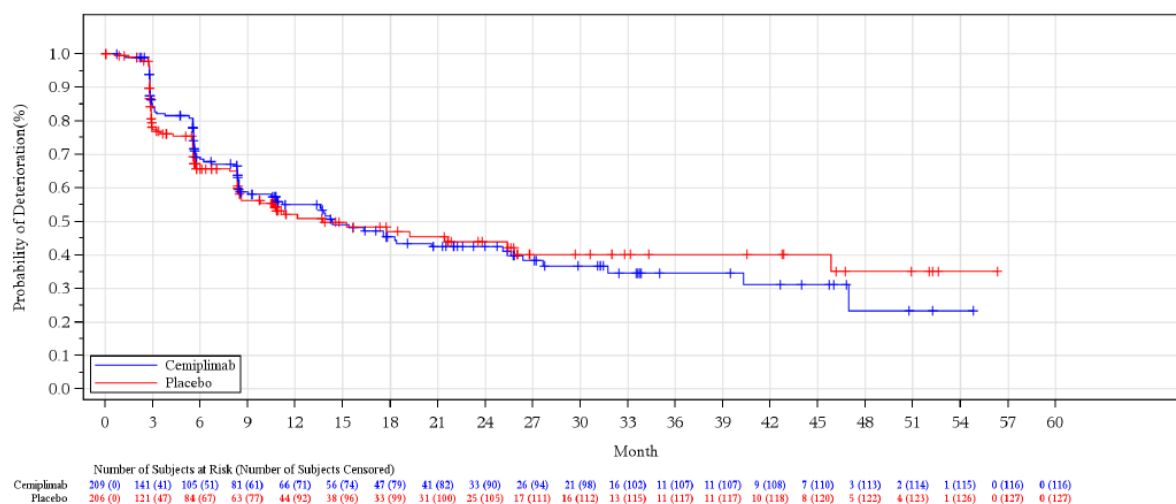


Figure 17: Kaplan-Meier curves on the outcome social functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)

I Appendix B Results on side effects

For AEs, SAEs and severe AEs (e.g. CTCAE grade ≥ 3) the following tables present proportions of events for SOC and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA), each based on the following criteria:

- AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- Additionally for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 18: Common AEs^a – RCT, direct comparison: cemiplimab vs. placebo (multipage table)

Study SOC ^b PT ^b	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
C-POST		
Overall AE rate	187 (91.2)	182 (89.2)
Skin and subcutaneous tissue disorders	111 (54.1)	85 (41.7)
Pruritus	33 (16.1)	25 (12.3)
Rash	33 (16.1)	18 (8.8)
Rash maculo-papular	23 (11.2)	12 (5.9)
Actinic keratosis	20 (9.8)	16 (7.8)
Infections and infestations	87 (42.4)	78 (38.2)
COVID-19	15 (7.3)	18 (8.8)
Skin infection	6 (2.9)	11 (5.4)
General disorders and administration site conditions	75 (36.6)	73 (35.8)
Fatigue	45 (22.0)	44 (21.6)
Oedema peripheral	11 (5.4)	5 (2.5)
Asthenia	10 (4.9)	7 (3.4)
Gastrointestinal disorders	73 (35.6)	72 (35.3)
Diarrhoea	32 (15.6)	38 (18.6)
Nausea	15 (7.3)	13 (6.4)
Constipation	12 (5.9)	17 (8.3)
Dry mouth	11 (5.4)	8 (3.9)
Musculoskeletal and connective tissue disorders	61 (29.8)	53 (26.0)
Arthralgia	26 (12.7)	25 (12.3)
Back pain	11 (5.4)	8 (3.9)
Nervous system disorders	46 (22.4)	45 (22.1)
Headache	14 (6.8)	18 (8.8)
Dysgeusia	10 (4.9)	0 (0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	44 (21.5)	51 (25.0)
Bowen's disease	16 (7.8)	21 (10.3)
Squamous cell carcinoma of the skin	16 (7.8)	20 (9.8)
Basal cell carcinoma	14 (6.8)	16 (7.8)
Investigations	39 (19.0)	23 (11.3)
Alanine aminotransferase increased	12 (5.9)	3 (1.5)
Aspartate aminotransferase increased	10 (4.9)	1 (0.5)
Endocrine disorders	33 (16.1)	7 (3.4)
Hypothyroidism	24 (11.7)	6 (2.9)
Hyperthyroidism	12 (5.9)	1 (0.5)

Table 18: Common AEs^a – RCT, direct comparison: cemiplimab vs. placebo (multipage table)

Study SOC ^b PT ^b	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
Metabolism and nutrition disorders	30 (14.6)	17 (8.3)
Injury, poisoning and procedural complications	29 (14.1)	25 (12.3)
Respiratory, thoracic and mediastinal disorders	29 (14.1)	26 (12.7)
Cough	12 (5.9)	7 (3.4)
Vascular disorders	20 (9.8)	19 (9.3)
Hypertension	8 (3.9)	11 (5.4)
Psychiatric disorders	17 (8.3)	14 (6.9)
Insomnia	11 (5.4)	5 (2.5)
Ear and labyrinth disorders	16 (7.8)	17 (8.3)
Renal and urinary disorders	16 (7.8)	10 (4.9)
Eye disorders	14 (6.8)	10 (4.9)
Blood and lymphatic system disorders	12 (5.9)	11 (5.4)
Cardiac disorders	11 (5.4)	8 (3.9)
Hepatobiliary disorders	10 (4.9)	2 (1.0)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 27.0; SOC and PT notation taken from Module 4 without adaptation. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 19: Common SAEs^a – RCT, direct comparison: cemiplimab vs. placebo

Study SOC ^b PT ^b	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
C-POST		
Overall SAE rate	36 (17.6)	19 (9.3)
Infections and infestations	10 (4.9)	9 (4.4)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 27.0; SOC notation taken from Module 4. MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class		

Table 20: Common severe AEs (CTCAE grade ≥ 3)^a – RCT, direct comparison: cemiplimab vs. placebo

Study SOC ^b PT ^b	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
C-POST		
Overall rate of severe AEs (CTCAE grade ≥ 3)	49 (23.9)	29 (14.2)
Infections and infestations	10 (4.9)	11 (5.4)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 27.0; SOC notation taken from Module 4. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 21: Discontinuation due to AEs – RCT, direct comparison: cemiplimab vs. placebo (multipage table)

Study SOC ^a PT ^a	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
C-POST		
Overall rate of discontinuations due to AEs	20 (9.8)	3 (1.5)
Skin and subcutaneous tissue disorders	4 (2.0)	0 (0)
Immune-mediated dermatitis	1 (0.5)	0 (0)
Pemphigoid	1 (0.5)	0 (0)
Rash	1 (0.5)	0 (0)
Skin ulcer	1 (0.5)	0 (0)
Investigations	3 (1.5)	0 (0)
Alanine aminotransferase increased	3 (1.5)	0 (0)
Aspartate aminotransferase increased	2 (1.0)	0 (0)
Blood alkaline phosphatase increased	2 (1.0)	0 (0)
Gamma-glutamyltransferase increased	1 (0.5)	0 (0)
Endocrine disorders	2 (1.0)	0 (0)
Adrenal insufficiency	2 (1.0)	0 (0)
Gastrointestinal disorders	2 (1.0)	0 (0)
Colitis	1 (0.5)	0 (0)
Immune-mediated enterocolitis	1 (0.5)	0 (0)
Musculoskeletal and connective tissue disorders	2 (1.0)	0 (0)
Arthralgia	1 (0.5)	0 (0)
Myositis	1 (0.5)	0 (0)
Cardiac disorders	1 (0.5)	0 (0)
Myocarditis	1 (0.5)	0 (0)
General disorders and administration site conditions	1 (0.5)	0 (0)
Fatigue	1 (0.5)	0 (0)
Hepatobiliary disorders	1 (0.5)	0 (0)
Immune-mediated hepatitis	1 (0.5)	0 (0)
Infections and infestations	1 (0.5)	0 (0)
Urinary tract infection	1 (0.5)	0 (0)
Injury, poisoning and procedural complications	1 (0.5)	0 (0)
Infusion related reaction	1 (0.5)	0 (0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.5)	3 (1.5)
Dedifferentiated liposarcoma	1 (0.5)	0 (0)
Acute myeloid leukaemia	0 (0)	1 (0.5)
Hepatocellular carcinoma	0 (0)	1 (0.5)

Table 21: Discontinuation due to AEs – RCT, direct comparison: cemiplimab vs. placebo (multipage table)

Study SOC ^a PT ^a	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
Lung neoplasm malignant	0 (0)	1 (0.5)
Renal and urinary disorders	1 (0.5)	0 (0)
Acute kidney injury	1 (0.5)	0 (0)
a. MedDRA version 27.0; SOC and PT notation taken unmodified from Module 5. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 22: Common immune-mediated AEs^a – RCT, direct comparison: cemiplimab vs. placebo

Study SOC ^b PT ^b	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
C-POST		
Overall rate of immune-mediated AEs	116 (56.6)	61 (29.9)
Skin and subcutaneous tissue disorders	78 (38.0)	38 (18.6)
Pruritus	29 (14.1)	19 (9.3)
Rash	26 (12.7)	13 (6.4)
Rash maculo-papular	23 (11.2)	10 (4.9)
Endocrine disorders	29 (14.1)	5 (2.5)
Hypothyroidism	22 (10.7)	5 (2.5)
Hyperthyroidism	11 (5.4)	0 (0)
Gastrointestinal disorders	25 (12.2)	19 (9.3)
Diarrhoea	21 (10.2)	17 (8.3)
Investigations	19 (9.3)	8 (3.9)
Alanine aminotransferase increased	11 (5.4)	3 (1.5)
Aspartate aminotransferase increased	10 (4.9)	1 (0.5)
Musculoskeletal and connective tissue disorders	13 (6.3)	11 (5.4)
Arthralgia	10 (4.9)	10 (4.9)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 27.0; SOC and PT notation taken from Module 5 without adaptation. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 23: Common immune-mediated SAEs – RCT, direct comparison: cemiplimab vs. placebo

Study SOC PT	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
C-POST		
Overall rate of immune-mediated SAEs^b	19 (9.3)	1 (0.5)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. For SAEs, no MedDRA SOC and PTs met the criterion for presentation. MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class		

Table 24: Common immune-mediated severe AEs (CTCAE grade ≥ 3)^a – RCT, direct comparison: cemiplimab vs. placebo

Study SOC ^b PT ^b	Patients with event n (%)	
	cemiplimab N = 205	placebo N = 204
C-POST		
Overall rate of immune-mediated severe AEs^b	19 (9.3)	1 (0.5)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. For severe AEs, no MedDRA SOC and PTs met the criterion for presentation. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

The full report (German version) is published at
<https://www.iqwiq.de/en/projects/a25-155.html>