Medicinrådet

Bilag til Medicinrådets vurdering af cemiplimab til adjuverende behandling af kutant planocellulært karcinom (CSCC) hos patienter med høj risiko for tilbagefald efter operation og strålebehandling

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. cemiplimab
2. Amgros' forhandlingsnotat vedr. cemiplimab
3. Ansøgning vedr. cemiplimab

We appreciate the efforts of the Danish Medicines Council (DMC) in reviewing the submission of cemiplimab for adjuvant treatment of cutaneous squamous cell carcinoma (CSCC) after surgery and radiotherapy. We would like to clarify the following points from the assessment report, as well as correct a factual mistake.

The relevance of disease-free survival and overall survival outcomes

As referenced in Section 3.7 of the submission, disease-free survival (DFS) after definitive treatment with curative intent, is frequently used as a primary outcome in oncologic clinical trials since the endpoint is available much earlier than overall survival (OS). DFS is less influenced than OS by competing causes of death and is not influenced by treatments administered after disease progression, considerations highly relevant in the current submission.

In planning the C-POST study, 3-year OS in the control arm was expected to be ≥80%, based on the results of a previous study (TROG 05.01). However, in the C-POST study, the control arm had the option to receive subsequent cemiplimab treatment upon disease recurrence and as such, OS of patients in the control arm of C-POST was expected to be better than what was observed in the TROG 05.01 study.

Conservatively assuming an OS of 80% at the end of the 3 years in the control arm, a median OS of 9 years was estimated. Even advanced CSCC (aCSCC) patients treated with cemiplimab under current standard practice see a 20-month survival of approximately 80%, highlighting the long survival times experienced by both recurrent and non-recurrent CSCC patients and the difficulties in drawing any meaningful conclusion from OS data at this stage. Nonetheless, the most recent C-POST data cut (April 2025) shows an improved hazard ratio for OS, and narrower confidence intervals for cemiplimab vs. placebo (HR 0,78 [95% CI: 0,39-1,56]) than the October 2024 data cut (HR 0,86 [95% CI: 0,39-1,90]).

While we agree with the assessment report's conclusion that no statistically significant impact on OS can be ascertained from the C-POST data at this stage, there are highly valid and robust reasons to consider DFS the most informative endpoint in this assessment and the best indicator available of the efficacy of cemiplimab in this population.

The comparability of treatment effects of cemiplimab in the curative adjuvant setting vs. the palliative recurrent setting (current practice)

Once patients reach the aCSCC stage they qualify for cemiplimab treatment under current Danish clinical practice. At this stage, treatment is no longer curative but palliative. Only 50% of these patients experience a durable response to anti-PD-1 therapy[1] and aCSCC patients overall face not only a lower OS than primary CSCC

[1] Rischin et al., 2025 Adjuvant Cemiplimab or Placebo in High-Risk Cutaneous Squamous-Cell Carcinoma
[2] Medicinrådet: Cemiplimab – Lokalt avanceret og metastatisk CSCC

patients but also lower health-related quality of life, sustaining a moderate to large impact on pain-related quality of life[2].

In addition, disease recurrence can lead to evident disfigurement with a high proportion of CSCC tumours appearing on the head and neck. Therefore, the reduced risk of CSCC recurrence with adjuvant cemiplimab, as acknowledged in the assessment report, is clinically meaningful for patients at high risk for recurrence from multiple perspectives.

Factual error in the assessment report

In Table 1 of the assessment report, under the efficacy measure of survival (Overlevelse / Død pga. Sygdomsprogression), it is reported that 12 patients from the cemiplimab arm died due to disease progression. This is not correct, as the number of deaths is 4 (see Section 6.1.4.6 of the submission dossier, second paragraph).

'A total of 25 deaths had occurred as of DCO1 (Oct 2024, Figure 11): 12 deaths (4 in the cemiplimab group and 8 in the placebo group) were due to disease progression and 13 deaths (8 in the cemiplimab group and 5 in the placebo group) were due to other causes.'

[1] Rischin et al., 2025 Adjuvant Cemiplimab or Placebo in High-Risk Cutaneous Squamous-Cell Carcinoma
[2] Medicinrådet: Cemiplimab – Lokalt avanceret og metastatisk CSCC

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25.02.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.03.2026
Leverandør	Regeneron Ireland
Lægemiddel	Libtayo (cemiplimab)
Ansøgt indikation	Cemiplimab til adjuverende behandling af voksne patienter med kutant planocellulært karcinom (CSCC) med høj risiko for tilbagefald efter kirurgi og strålebehandling
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Libtayo (cemiplimab):

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Libtayo	350 mg (1 stk.)	36.074,28	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale på Libtayo. Aftalen løber indtil 31.12.2026 med mulighed for forlængelse. Der er inkluderet mulighed for prisregulering i aftalen. Aftalen på Libtayo kører sammen med de øvrige immunterapier.

Konkurrencesituationen

Kirurgisk fjernelse af tumoren med helbredende sigte er førstevalg ved behandling af højrisiko kutant planocellulært karcinom. Stråleterapi kan anvendes som et alternativ til patienter, som ikke kan gennemføre eller ikke ønsker kirurgisk behandling. Libtayo er det eneste medicinske alternativ til patientpopulationen.

Tabel 2 viser lægemiddeludgifter til Libtayo for 24 ugers behandling, jf. Medicinrådets Tværgående omkostningsanalyse for PD(L)1-hæmmere.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 24 uger (SAIP, DKK)
Libtayo (cemiplimab)	350 mg (1 stk.)	350 mg hver 3. uge i 12 uger (4 serier), herefter 700 mg hver 6. uge, i.v.	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
England	Under vurdering	Link til status
Sverige	Under vurdering	Link til status

Opsummering

Libtayo indgår i udbuddet på immunterapier. Leverandøren har derfor kun mulighed for at sænke deres pris ved en aktivering af prisreguleringsmekanismen. Der er aktuelt ikke planlagt en prisregulering indenfor immunterapien.

Application for the assessment of cemiplimab for the adjuvant treatment of adult patients with cutaneous squamous cell carcinoma at high risk of recurrence after surgery and radiation therapy

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

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Table of contents

Tables and Figures

Abbreviations

Abbreviation	Full name
CI	Confidence intervals
CSCC	Cutaneous squamous cell carcinoma
DCO	Data cutoff
DFS	Disease-free survival
DK	Denmark
DMCG	Danish multidisciplinary cancer group
DR	Distant recurrence
EADO	European association of dermato-oncology
ECE	Extracapsular extension
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
FFDR	Freedom from distant recurrence
EORTC QLQ-C30	European; Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	EuroQOL Five Dimensions Questionnaire 5L
FFLRR	Freedom from locoregional recurrence
GHS	Global health status
HE	Health-economic
HN	Head and neck
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ITT	Intention to treat
KM	Kaplan-Meier
KOL	Key opinion leader
LRR	Locoregional recurrence

LS	Least squares
MMRM	Mixed effect models for repeated measures
NE	Not established
NR	Not reached
OS	Overall survival
PH	Proportional hazard
PNI	Perineural invasion
PRO	Patient reported outcome
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
ROW	Rest of world
RT	Radiotherapy
SAF	Safety analysis full set
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SPT	Second primary tumour
TEAE	Treatment-emergent adverse events
VAS	Visual analog scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Libtayo
Generic name	Cemiplimab
Therapeutic indication as defined by EMA	Adjuvant Cemiplimab for the treatment of adult patients with cutaneous squamous cell carcinoma (CSCC) at high risk of recurrence after surgery and radiation.
Marketing authorization holder in Denmark	Regeneron Ireland
ATC code	L01FF06
Combination therapy and/or co-medication	None
Date of EC approval	19 November 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	• Cutaneous Squamous Cell Carcinoma (1): LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation. • Basal Cell Carcinoma (1): LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI). • Non-Small Cell Lung Cancer (1): LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

Overview of the medicine	
	○ locally advanced NSCLC who are not candidates for definitive chemoradiation, or ○ metastatic NSCLC. • LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have: ○ locally advanced NSCLC who are not candidates for definitive chemoradiation, or ○ metastatic NSCLC. • Cervical Cancer (1): LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.
Other indications that have been evaluated by the DMC (yes/no)	• Lung cancer: 1st line treatment of non-small cell lung cancer with PD-L1 > 1% (2) • Lung cancer: Incurable Non-Small Cell Lung Cancer With PD-L1 Expression > 50% (3) • CSCC: Locally advanced and metastatic cutaneous squamous cell carcinoma (4) • Basal cell carcinoma (5)
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? **Yes** Is the product suitable for a joint Nordic assessment? **No** If no, why not? **There are different, simplified procedures available in each Nordic country for PD-(L)1 therapies which are more suitable than JNHB.**
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	LIBTAYO 350 mg concentrate for solution for infusion (6)

2. Summary table

Summary	
Indication relevant for the assessment	Adjuvant Cemiplimab for the treatment of adult patients with cutaneous squamous cell carcinoma (CSCC) at high risk of recurrence after surgery and radiation (1).
Dosage regiment and administration	The recommended dose of cemiplimab administered as an intravenous infusion over 30 minutes is: • 350 mg every 3 weeks for 12 weeks followed by 700 mg every 6 weeks, or • 350 mg every 3 weeks Treatment may be continued until disease recurrence, unacceptable toxicity, or up to 48 weeks of total therapy (1).
Choice of comparator	Placebo

Prognosis with current treatment (comparator)	The first-choice treatment for high-risk tumours is surgical treatment or radiation therapy. a) Surgical excision is the first choice in the treatment of high-risk CSCC. Radiation therapy can be used as an alternative. The first choice treatment for low-risk tumours is surgical treatment or radiation therapy (7).
	Prognosis:
	• General: Even though it is a malignant disease, the 5-year survival rate is > 90%. In 2014, 36 men and 23 women died from this disease in Denmark (7)
	• The prognosis depends on localization, size, histological pattern, depth of invasion, perineural involvement, and whether the patient is immunosuppressed (7)
	• Lesions less than 2 cm versus lesions over 2 cm have (7)
	  ○ 6% vs 16% recurrence rate
	  ○ 8% vs 23% metastasis rate
	• Total metastasis risk of CSCC has been found to be (7)
	  ○ On-ear 11%
	  ○ On the lip 14%
	  ○ Other locations 5 %
	Despite the favourable prognosis of localized CSCC, disease progression fundamentally alters the clinical picture. Once CSCC advances, patient outcomes deteriorate. Making prevention of recurrence and metastasis a critical therapeutic priority.
	
	Advanced, locally advanced, metastatic (8):
	Advanced cutaneous squamous cell carcinoma (aCSCC) is defined as either locoregional disease (laCSCC) or distant metastatic disease (mCSCC) that is not amenable to treatment with surgery or radiotherapy. Advanced CSCC

Summary	
	often occurs in the head and neck region, where surgical treatment can result in significant functional and cosmetic impairment. The median age is estimated to be 78 years An estimate of median survival in patients with aCSCC is 16-17 months with a 1-year survival rate (OS rate) of 59-65%, 2-year OS rate of 37-41%, and a 3-year OS rate of 24-26%. Survival rates for laCSCC are more difficult to elucidate but are estimated to have a median survival of 53 months, a 1-year OS rate of 92%, a 2-year OS rate of 77%, and a 3-year OS rate of 71%. To date, cemiplimab is the only approved standard systemic treatment for patients with aCSCC in Europe. Chemotherapy has primarily been platinum- or taxane-based combination therapy (9).
Type of evidence for the clinical evaluation	Head-to-head: C-POST Study: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study of Adjuvant Cemiplimab Versus Placebo After Surgery and Radiation Therapy in Patients With High Risk Cutaneous Squamous Cell Carcinoma (10).
Most important efficacy endpoints (Difference/gain compared to comparator)	Relevant primary: Median disease-free survival (DFS): HR 0.32 (95% CI: 0.20 – 0.51) Relevant secondary: Median freedom from locoregional recurrence (FFLRR): HR 0.20 (95% CI: 0.09 – 0.40) Median freedom from distant recurrence (FFDR): HR 0.35 (95% CI: 0.17 – 0.72) Relevant tertiary: HRQoL, as assessed by the EORTC QLQ-C30. General health status and health utility, as assessed using the EQ-5D-3L (10, 11).
Most important serious adverse events for the intervention and comparator	Serious TEAEs (by PT) reported in ≥1.0% of patients in the cemiplimab arm versus the placebo arm were: Pneumonia (1.0% versus 1.0%), Adrenal insufficiency (1.0% versus 0%), and Diarrhoea (1.0% versus 0%) (11).
Impact on health-related quality of life	More than 88% of the patients in each group completed the EORTC QLQ-C30 at baseline and through all the cycles. The overall change from baseline in EORTC QLQ-C30 global health status– quality of life scores across all time points during the treatment period indicated no meaningful between-group difference (difference in the least squares mean change, −0.94 points [95% CI, −3.65 to 1.77]; clinically meaningful change, ≥10 points). Maintenance of the global

Summary	
	health status–quality of life scores appeared to be sustained after the treatment period (10).
Type of economic analysis that is submitted	NA. Given the 14-week process, no economic analysis will be submitted
Data sources used to model the clinical effects	NA. Given the 14-week process, no model will be submitted
Data sources used to model the health-related quality of life	NA. Given the 14-week process, no model will be submitted
Life years gained	NA. Given the 14-week process, no model will be submitted
QALYs gained	NA. Given the 14-week process, no model will be submitted
Incremental costs	NA. Given the 14-week process, no model will be submitted
ICER (DKK/QALY)	NA. Given the 14-week process, no model will be submitted
Uncertainty associated with the ICER estimate	NA. Given the 14-week process, no model will be submitted
Number of eligible patients in Denmark	Incidence: Approximately 2600 patients diagnosed in 2024 (12). Prevalence: 612.9 per 100,000 in 2023 were diagnosed with non-melanoma skin cancer, excluding basal cell carcinoma (13). 16 patients per year are estimated to be eligible for cemiplimab under this indication (Table 2, Table 3).
Budget impact (in year 5)	NA. Given the 14-week process, no model will be submitted

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

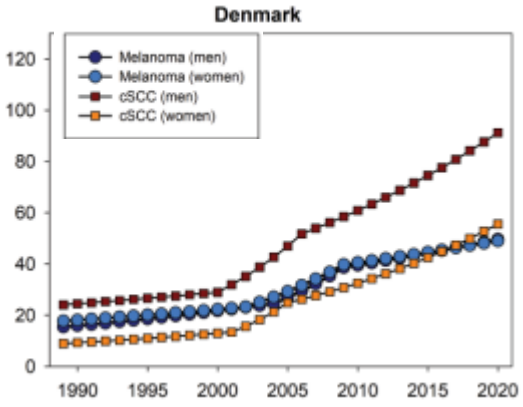
3.1 The medical condition

Cutaneous squamous cell carcinoma (CSCC) is the second most common non-melanoma skin cancer, estimated to affect over 2.4 million patients per year globally (14, 15). CSCC is a keratinocyte-derived tumour that usually arises from pre-malignant lesions, such as actinic keratosis or Bowen disease, and most often presents as a nodule or an ulcer that does not heal. The most common genetic abnormalities observed in CSCC represent pathways involved in cell cycle regulation, apoptosis and signalling pathways. The most common individual mutation in CSCC is in the TP53 tumour suppressor gene (16).

The clinical presentation of CSCC is highly variable, with a persistent ulcer or non-healing wound generally present (17). Most primary CSCC (80-90%) are located on the head and neck (18). Patients with CSCC may experience disease-related pain and/or changes to appearance; additionally, surgery and/or RT may cause disfigurement, loss of function, and/or other complications (19). The morbidity associated with CSCC may negatively affect health-related quality of life (HRQoL) (20).

There are many risk factors for CSCC, including ultraviolet (UV) exposure (especially UVB), male sex, fair skin, older age, and genetic predisposition (15, 21). Immunosuppression is also an important risk factor; particularly immune suppression associated with organ transplant (21). In Denmark, it is estimated around 2600 people are diagnosed with CSCC every year, though incidence has been steadily increasing in Denmark over the past 20 years (22). Most CSCC patients have a favourable prognosis; the 5-year survival rate is over 90%, and 60 Danes are estimated to die every year from CSCC (7, 12). Mortality after curative surgery is 4.1% (7).

Figure 1 Age-standardised rate (ASR, per 100k population) of skin cancers in Denmark



Source: Olsen et al. (22)

Surgical resection is the centrepiece of clinical management of CSCC, and the cure rate following surgical excision and/or radiotherapy (RT) is estimated to be over 90% (23). The use of adjuvant RT for patients at high risk of CSCC recurrence is supported by some retrospective CSCC studies (9). Despite this, a subset of patients with CSCC have disease recurrence, either locoregional or distant, after undergoing surgery and receiving adjuvant radiotherapy (24).

A small fraction of patients with CSCC are considered to have increased risk of CSCC recurrence after surgery due to nodal features (extracapsular extension or ≥ 3 involved lymph nodes) and/or non-nodal features (in-transit metastases, T4 lesion, perineural invasion, or locally recurrent tumour with ≥ 1 additional adverse feature) (1, 10).

In CSCCs overall, the proportion of local recurrence is ~3%–5% and the proportion of nodal metastasis is ~3%–5%. However, in CSCCs with high-risk features, the frequency of local recurrence may increase up to 30% and the frequency of metastasis may increase up to 35% (25). Mortality and survival data around CSCC and, in particular, advanced CSCC, is scarce and limited by underreporting and grouped classifications with basal cell carcinomas (25). A German registry study found the relative 5-year survival of overall CSCC to be 94%, with 5-year survival dropping to 58.3% for CSCC with regional metastasis (25, 26). In a Norwegian registry study, 5-year survival rates for localised CSCC were found to be 88% and 82% for women and men respectively, while this dropped to 64% and 51% for advanced CSCC (25, 27).

Patients with high-risk CSCC that undergo disease recurrence not only suffer significantly worsened survival rates (28) but also high clinical and economic burden, as they typically require subsequent treatment for recurrent or advanced CSCC (e.g. systemic therapy, additional surgery, RT), which negatively affect HRQoL and increase treatment-related healthcare resource utilisation and costs (9, 29-32). The substantial burden associated with recurrence and metastasis highlights the need for additional proactive intervention following surgery in patients with CSCC at high-risk of recurrence. There remains a high unmet need for an adjuvant treatment that can delay or prevent recurrence among patients with high-risk CSCC, thereby delaying or preventing the need for subsequent use of additional systemic treatments and improving survival.

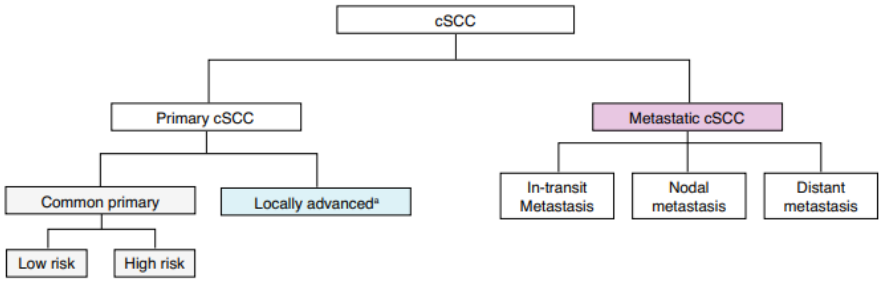
3.2 Patient population

Incidence and prevalence data is often flawed for CSCC, possibly due to inclusion of actinic keratosis and in situ SCC in the data (18). Large differences for example, can be seen in both incidence and prevalence of CSCC in the Danish population between Guo et al. (14), Olsen et al. (22) and Hudkræftdatabasen (33).

Table 1 presents the incidence and prevalence data found in the 2023/24 Hudkræftdatabasen Årsrapport. The heterogeneity in CSCC incidence and prevalence data is acknowledged in the wider literature (17, 18), though there is consensus regardless that the incidence is growing among white populations globally and in Denmark specifically (14, 18, 33). Age standardised incidence, prevalence and mortality for the Danish population between 1990-2019 has increased by 5.1% (95% CI: -9.8% - 21.5%), 5.3% (-9% - 21.3%) and 86.9% (95% CI: 26.9% - 110.1%) respectively (14), while the proportion of the Danish population diagnosed each year with CSCC rose from 0.24% in 2019/20 to 0.38% in 2023/24 (33).

Due to the high cure rate following surgical excision and/or radiotherapy, evaluated to be around 95% (23), and over 98% in dermatologically-treated patients (presumed low-risk by Hudkræftdatabasen) in Denmark (33), this submission applies only to the high-risk CSCC subgroup. This subset of CSCC patients have higher risk of disease recurrence, either locoregional or distant, after undergoing surgery and receiving adjuvant radiotherapy.

Figure 2 Classification of invasive CSCCs



Source: Dessinioti et al, 2022 (25).
(a) Locally advanced CSCC is by definition not amenable to curative surgery and/or RT.

Table 1 Incidence and prevalence of CSCC in Denmark, over the past 5 years

Year	2019/20	2020/21	2021/22	2022/23	2023/24
Incidence in Denmark: Patients diagnosed per year (33)	1.382	1.548	1.646	1.880	2.272
Prevalence in Denmark, per 100,000 [a][b] (13, 33, 34)	445.3	486.8	528.2	568	612.9

Year	2019/20	2020/21	2021/22	2022/23	2023/24
Global prevalence, per 100,000 *(14)	39.3 (95% CI: 34 – 45.8)	NA	NA	NA	NA

* For small patient groups, also describe the worldwide prevalence.
[a] Prevalence is based on NORDCAN data for non-melanoma skin cancers, excluding basal cell carcinomas. This categorisation includes Bowen's disease and actinic keratosis.
[b] Prevalence data exclusive to CSCC was not identified from local sources (NORDCAN, Hudkræftdatabasen). These sources are considered more accurate than global studies and so are used despite the overlapping categorisation.
Sources: Hudkræftdatabasen Årsrapport (35, 36), NORDCAN (13)

3.2.1 Defining the high-risk CSCC population in Denmark

Danish clinical practice largely follows EADO (European Association of Dermato-Oncology) guidelines on defining high-risk CSCC (18), with the Danish clinical practice guidelines for categorising high-risk CSCC requiring 1 or more of the following: (7):

a) Tumour size ≥ 2 cm in diameter

b) Location: Lip, ear, perineum, perianal or genital

c) Immunosuppressed patient

d) Recurrence of tumour

e) Tumour occurring in chronically damaged skin such as Marjolins ulcus, osteomyelitis, scars, burns or radiation-damaged skin

f) Histology: Low degree of differentiation, Tumour thickness >2 mm, Invasion into deep dermis or subcutis (Clark level IV and V), Perineural, perivascular or perilymphatic invasion, Tumour depth is related to risk of metastasis.

Defining the actual high-risk CSCC population eligible for adjuvant cemiplimab specific to Denmark is difficult, however, as classification of CSCC populations by risk status is not found in country-specific epidemiological resources. Furthermore, the definition of high-risk CSCC is variable across guideline recommendations, so estimates of high-risk CSCC vary between countries and can't confidently be extrapolated.

Denmark's Hudkræftdatabasen (33) for example, suggests the roughly 45% of CSCC patients in Denmark who are referred for more specialist treatment in hospitals (N=1629 in 2023/24), are those at high-risk (33). This suggestion is limited as it is not evidenced by any data beyond patient referral for more specialist treatment. It is also important to note that the Danish criteria for 'high-risk' CSCC, unlike the criteria used in the C-POST trial, includes common risk factors such as tumour size >2cm in diameter and immunosuppression. In a published review of more than 23,000 resected CSCCs, these two risk factors were found in 49.1% and 27% of CSCC cases that went on to recur or metastasise, demonstrating their prevalence in the high-risk classification. For this reason, it is reasonable to expect the proportion of 'high-risk' CSCCs by Danish definition to far exceed that of the more narrowly defined C-POST trial.

In the absence of Denmark-specific registry data describing the number of patients with high-risk CSCC, estimates for the proportion of patients with CSCC who have high-risk disease can be derived from the limited literature in CSCC that best aligns with high-risk features from the C-POST study, including nodal (eg, nodal disease with ECE) and non-nodal (eg, PNI, in-transit metastases, T4 tumours, and recurrent CSCC) features. This estimation is therefore constructed using international data:

1) Granger et al. (2024) found that 1.5% of CSCC patients developed nodal metastases (nodal disease) (37).
2) Further stratification data from Ebrahimi et al. (2020), a study focused on staging head and neck CSCC, indicated that 81% of patients with nodal disease had ECE, with the median maximum nodal size of 2.5 cm (38).
3) To account for non-nodal high-risk patients, the nodal high-risk population is multiplied by a factor of 1.7 using the C-POST patient distribution (11).

From these, we estimate the high-risk CSCC subgroup, as categorised in the C-POST study, to comprise approximately 2% of all CSCC incident cases. Of this 2% high-risk population, 60% are expected to have received RT and therefore be eligible for cemiplimab in this setting (39-41). The inputs are described in Table 2 below.

Table 2 Epidemiological inputs used in estimating eligible number of patients in Denmark

Parameter	Value
Population of Denmark (42)	6,000,000
Proportion of Danish population diagnosed with CSCC (3-year average) (35)	0.033%
Annual growth rate in the number of CSCC cases in Denmark (14)	5.00%
Proportion of CSCC patients in Denmark who undergo resection (35)	54.90%
Proportion of resected CSCC patients who are at high risk of recurrence (11, 37, 38)	2.07%
Proportion of resected high-risk CSCC patients who receive radiotherapy (39-41)	60%
Estimated number of eligible patients in Denmark, annually	16

At an incidence growth rate of 5% (14), the number of patients eligible for treatment with cemiplimab in this indication is not expected to change over the coming 5 years (Table 3).

Table 3 Estimated number of patients eligible for treatment in Denmark

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	16	16	16	16	16

3.3 Current treatment options

Treatment goals in Denmark are primarily to treat with surgical excision (curative in 95% of CSCC cases (23)) where possible and radiotherapy as the primary alternative. Advanced CSCC, categorised by tumours not amenable to curative treatment by surgery or radiotherapy, can be treated pharmaceutically with cemiplimab (3, 7). Curettage and electrocautery is often used in low-risk tumour treatment (33).

For high-risk tumours, the first line treatment is surgical excision, with radiotherapy an option post-operatively, as an adjuvant, or as an alternative altogether when surgery is not an option. Watching and waiting is not recommended (7).

Surgical excision on high-risk tumours should be performed with a 6-10mm safety margin to the visible tumour and to subcutaneous fat at the base of the specimen. If this is not possible, adjuvant radiotherapy should be considered. Surgical excision of high-risk tumours of the face can be particularly challenging, and micrographically controlled surgery may be considered in these cases (7, 9). Prognosis depends on location, size, histological pattern, depth of invasion, perineural involvement and whether the patient is immunosuppressed. For example, lesions smaller than 2cm vs. lesions larger than 2 cm have (7):

- 6% vs 16% recurrence rate
- 8% vs 23% metastasis rate

In cases where surgical excision is not possible, curative primary definitive radiotherapy can be used as a valid curative treatment option. A 2013 meta-analysis reported a pooled average local recurrence rate of 6.4%, following radiotherapy treatment of primary CSCC (43).

The use of adjuvant radiotherapy in Denmark is not clear, and it is known to vary heavily by country; KOL research conducted by Regeneron found the average adjuvant RT use among patients high-risk CSCC ranged from 12% (Germany) to 35% (Spain) across 6 European countries. Denmark was not one of the countries included in this research (44).

Adjuvant radiotherapy has however, not yet been shown to provide significant benefit to the high-risk CSCC group; a patient group with a clear unmet need (9).

There are no DMCG guidelines for CSCC treatment in Denmark.

3.4 The intervention

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

Overview of intervention (1)	
Indication relevant for the assessment	Adjuvant Cemiplimab for adult patients with cutaneous squamous cell carcinoma (CSCC) at high risk of recurrence after surgery and radiation therapy.
ATMP	No.
Method of administration	IV Infusion.
Dosing	350mg every 3 weeks for up to 48 weeks OR 350mg every 3 weeks for 12 weeks, followed by 700mg every 6 weeks for up to 36 weeks (1, 10, 45).
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Up to 48 weeks or until disease recurrence or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	Standard monitoring for IO therapies. Refer to section 4.4 of the SmPC (1).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	None. No model is included in this submission.
Package size(s)	LIBTAYO 350 mg concentrate for solution for infusion (6)

3.4.1 Description of ATMP

N/A. Cemiplimab is not an ATMP.

3.4.2 The intervention in relation to Danish clinical practice

The adjuvant treatment of adult CSCC patients at high risk of recurrence with cemiplimab is indicated only after surgery and radiotherapy. Adjuvant cemiplimab would therefore only be used alongside the current standard of care for high-risk CSCC and not directly displace any therapies from the treatment algorithm. However, in reducing the likelihood of disease recurrence, adjuvant cemiplimab treatment is expected to reduce the proportion of CSCC tumours progressing to advanced disease. This will reduce the use of subsequent therapies, including cemiplimab itself, as cemiplimab is currently the recommended standard in Denmark for the treatment of locally advanced or metastatic CSCC.

3.5 Choice of comparator(s)

Placebo is the comparator relative to Danish clinical practice in the submitted indication for adjuvant Cemiplimab in high-risk of recurrence CSCC patients following surgery and/or radiotherapy, as there are no alternatives evaluated by the DMC and no alternatives with definitive, proven clinical benefit beyond standard current practice (9, 46).

Overview of comparator	
Generic name	N/A - Placebo
ATC code	N/A
Mechanism of action	N/A
Method of administration	N/A
Dosing	N/A
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A

Overview of comparator	
Package size(s)	N/A

3.6 Cost-effectiveness of the comparator(s)

N/A.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 4 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Primary Outcome – Disease-free survival (DFS) C-POST study (10)	Median follow-up in this study was 24 months (range 2-64). Data cutoff 04. Oct. 2024.	Time from randomization to the first documented disease recurrence (local, regional and/or distant) by investigator assessment or death due to any cause, whichever first. For patients who did not have a tumour recurrence or death, DFS will be censored on the date of last disease assessment.	During the treatment period, radiologic assessments were performed at screening and at the end of each 12-week cycle. In the follow-up period, clinical and radiologic assessments were performed every 4 months for the first 2 years and every 6 months thereafter. KM plots were used for analysis.
Secondary Outcome – Freedom from locoregional recurrence (FFLRR) C-POST study (10)	Median follow-up in this study was 24 months (range 2-64). Data cutoff 04. Oct. 2024.	Time from randomization to the date of first LRR. Patients who died without a preceding LRR will be censored on the date of death. For patients who did not have a LRR or death, FFLRR will be censored on the date of last disease assessment.	During the treatment period, radiologic assessments were performed at screening and at the end of each 12-week cycle. In the follow-up period, clinical and radiologic assessments were performed every 4 months for the first 2 years and every 6 months thereafter. KM plots were used for analysis.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Secondary Outcome – Freedom from distant recurrence (FFDR) C-POST study (10)	Median follow-up in this study was 24 months (range 2-64). Data cutoff 04. Oct. 2024.	Time from randomization to the date of first DR. Patients who died without a preceding DR will be censored on the date of death. For patients who did not have a DR or death, FFDR will be censored on the date of last disease assessment.	During the treatment period, radiologic assessments were performed at screening and at the end of each 12-week cycle. In the follow-up period, clinical and radiologic assessments were performed every 4 months for the first 2 years and every 6 months thereafter. KM plots were used for analysis.
Secondary Outcome – Occurrence of second primary CSCC tumours (SPTs) C-POST study (11)	Median follow-up in this study was 24 months (range 2-64). Data cutoff 04. Oct. 2024.	Cumulative occurrence of SPTs for each patient from randomization to occurrence of first primary endpoint event or EOS.	During the treatment period, radiologic assessments were performed at screening and at the end of each 12-week cycle. In the follow-up period, clinical and radiologic assessments were performed every 4 months for the first 2 years and every 6 months thereafter.
Secondary Outcome - Overall survival (OS) C-POST study (10)		OS is defined as the time from randomization to death from any cause. A patient who has not died will be censored on the last known date as alive. Hypothesis testing is not performed because 3-year OS in the control arm is expected to be ≥80%, based on result of the TROG 05.01 study (24).	Patients in survival follow-up were contacted quarterly (telephone is acceptable) for survival status and treatment status (subsequent anticancer systemic therapy) until the final EOS that occurs when the required number of events to declare the primary endpoint of the study has been reached (47).
Health-Related Quality of Life (HRQoL)		HRQoL as assessed by the EORTC QLQ-C30 and EQ-5D-5L.	EORTC QLQ-C30 and EQ-5D-3L were administered at day 1 of every cycle, end of treatment, and

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
C-POST study (11)			during follow-up in Part 1. More detailed on analyses conducted in section 10.1.

* Time point for data collection used in analysis (follow up time for time-to-event measures).
Abbreviations: KM, Kaplan-Meier; LRR, locoregional recurrence; DR, distant recurrence; EOS, End of study, EORTC-QLQ-C30, European; Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, the EuroQOL Five Dimensions Questionnaire 5L.

Validity of outcomes

This submission relates to Cemiplimab as an adjuvant therapy to curative surgery and/or radiotherapy. Disease-free survival (DFS) after definitive treatment with curative intent is frequently used as a primary outcome in oncologic clinical trials because the endpoints are available earlier than OS, less influenced than OS by competing causes of death, and not influenced by treatments administered after progression (48) (49). DFS is often considered an important end-point for cancers with prolonged OS, and has been used as a strong surrogate endpoint for OS in oncologic clinical trials (49).

Regarding overall survival (OS), hypothesis testing is not performed because 3-year OS in the control arm is expected to be ≥80%, based on result of the TROG 05.01 study (24). In the C-POST study, the control arm has the option to receive subsequent cemiplimab treatment upon disease recurrence. As such, the OS of patients in the control arm of the proposed study is expected to be better than what was observed in the TROG 05.01 study and no worse than the OS of advanced CSCC patients treated with cemiplimab. In a recent efficacy update for advanced CSCC patients in pivotal Study R2810-ONC-1540 that was performed as part of the regulatory procedures at the time of the designing the study, the estimated OS for advanced CSCC patients treated with cemiplimab at 20 months was approximately 80% (11). Assuming an OS of 80% at the end of 3 years in the control arm, this translates into a median OS of 9 years. Therefore, only descriptive statistics are provided for OS.

4. Health economic analysis

4.1 Model structure

N/A – this section is not applicable as cemiplimab is a PD-1 inhibitor, per the DMC process guide for 14-week submissions.

4.2 Model features

N/A

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	N/A	N/A

5. Overview of literature

5.1 Literature used for the clinical assessment

A head-to-head study, C-POST, comparing adjuvant cemiplimab to placebo in high-risk cutaneous squamous-cell carcinoma was identified and thus a literature search was omitted, in accordance with the DMC methods guidelines (50).

Table 6 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Adjuvant Cemiplimab or Placebo in High-Risk Cutaneous Squamous-Cell Carcinoma. D. Rischin, S. Porceddu, F. Day, P. Brungs Daniel, H. Christie, E. Jackson James, et al. New England Journal of Medicine 2025 Vol. 393 Issue 8 Pages 774-785 DOI: 10.1056/NEJMoa2502449 (10)	C-POST	NCT03969004	Start: 04/06/2019 Completion: 26/03/2028 Data cut-off: 04/10/2024 Future data cut-offs: 07/04/2025	Adjuvant cemiplimab vs. placebo in high-risk cutaneous squamous-cell carcinoma.
Data on file. Clinical Study Report (R2810-ONC-1788 Primary Analysis) 2024 Regeneron Pharmaceuticals (11)	C-POST	NCT03969004	Start: 04/06/2019 Completion: 26/03/2028 Data cut-off: 04/10/2024 Future data cut-offs: 07/04/2025	Adjuvant cemiplimab vs. placebo in high-risk cutaneous squamous-cell carcinoma.

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life data was obtained solely from the head-to-head C-POST study. A health economic analysis has not been carried out and thus a literature search is not relevant.

Table 7 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Clinical study report (R2810-ONC-1788 Primary Analysis). Regeneron Pharmaceuticals Inc (11)	All HRQoL information referenced.	Section 10.1

5.3 Literature used for inputs for the health economic model

Not applicable – no health economic model carried out.

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of adjuvant Cemiplimab compared to placebo for adult patients with cutaneous squamous cell carcinoma (CSCC) at high risk of recurrence after surgery and radiation therapy.

6.1.1 Relevant studies

This application is built on the C-POST Study (NCT03969004): A phase 3 randomised, placebo-controlled, double-blind study of adjuvant cemiplimab versus placebo after surgery and radiation therapy in patients with high-risk cutaneous squamous cell carcinoma. This application targets the same pre-defined subpopulation as the C-POST study: CSCC patients at high risk of recurrence after surgery and radiation therapy.

Table 9 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
C-POST Study of adjuvant Cemiplimab versus placebo after surgery and radiation therapy in patients with high-risk cutaneous squamous cell carcinoma, NCT03969004 D. Rischin, S. Porceddu, F. Day, P. Brungs Daniel, H. Christie, E. Jackson James, et al. (10)	An ongoing, phase 3 randomized, double-blinded, placebo-controlled study of Cemiplimab versus placebo.	Up to 48 weeks double-blind followed by up to 96 weeks open label (for patients who have recurrence on the placebo arm or who completed Cemiplimab treatment in part 1 and recurred more than 3 months later. Study started in June 2019, with primary completion estimated for Nov. 2026, and study completion	Patients with local or regional cutaneous squamous-cell carcinoma, after surgical resection and postoperative radiotherapy, at high risk of recurrence.	Cemiplimab 350mg IV Q3W for 12 weeks, followed by 700mg IV Q6W for up to 36 weeks.	Placebo IV Q3W for 12 weeks, followed by Q6W for up to 36 weeks.	This study presents data from the first interim analysis, planned to take place after approximately 83 DFS events (50% of total DFS events), data-cutoff date 04.10.2024. The Lan-deMets O'Brien-Fleming spending function was used for type I error control. This analysis crossed the prespecified efficacy threshold for DFS and therefore became the primary analysis. A later, unpublished data cutoff of 07.04.2025 is presented in addition. Median follow-up in this study was 24 months (range 2-64). (10) Primary endpoint -Disease-free survival (DFS): time from randomization to the first documented disease recurrence by investigator assessment or death due to any cause, whichever first. Secondary endpoints -Freedom from locoregional recurrence (FFLRR) -Freedom from distant recurrence (FFDR) -Cumulative occurrence of second primary CSCC tumours (SPTs) -Overall survival (OS) -Safety, including treatment-emergent adverse events (TEAEs) Radiological assessments were performed at screening and at the end of each 12-week cycle during treatment. In the follow-up period, clinical and radiological

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
		estimated for Mar. 2028.				assessments were performed every 4 months for 2 years and every 6 months after. Tertiary endpoints -HRQoL as assessed by the EORTC QLQ-C30 and EQ-5D-5L

Abbreviations: Q3W, every 3 weeks; Q6W, every 6 weeks; EORTC-QLQ-C30, European; Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, the EuroQOL Five Dimensions Questionnaire 5L; HRQoL, Health-related quality of life.

6.1.2 Comparability of studies

Not relevant, C-POST study is head-to-head.

6.1.2.1 Comparability of patients across studies

From June 2019 through August 2024, a total of 526 patients at high risk for recurrence of cutaneous squamous-cell carcinoma underwent screening and 415 were randomly assigned to receive adjuvant therapy with cemiplimab (209 patients) or placebo (206). Among all the patients, the median age was 71 years (range, 33 to 95), 83.9% were men, and 82.7% had primary cutaneous squamous-cell carcinoma of the head and neck. The high-risk nodal disease category included 242 patients (58.3%). The most common high-risk criterion was extra-capsular extension in at least one node measuring at least 20 mm in diameter (in 48.4% of the patients). Overall, the demographic and disease characteristics of the patients at baseline were well balanced between the two trial groups.

The inclusion/exclusion criteria are described as follows:

Adult patients with high-risk CSCC who had undergone surgical resection followed by RT, with high-risk defined by at least 1 of the following:

- a. Nodal disease with (i) Extracapsular extension (ECE) and at least 1 node >20 mm on the surgical pathology report, and/or (ii) ≥3 lymph nodes positive on surgical pathology report, regardless of ECE.
    - *ECE is defined as extension through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. Unambiguous evidence of gross ECE (defined as invasion of skin, infiltration of musculature/fixation to adjacent structures on clinical examination) is a sufficiently high threshold to classify these as ECE positive (51).
- b. ITM, defined as skin or subcutaneous metastases that are >2 cm from the primary lesion but are not beyond the regional nodal basin (52).
- c. T4 lesion, including HN lesions (51) and non-HN lesions.
- d. Perineural invasion (PNI), defined as clinical and/or radiologic involvement of named nerves.
- e. Recurrent CSCC, defined as CSCC that arises within the area of the previously resected tumour, plus at least 1 of the following additional features (51):
    - • ≥N2b disease associated with the recurrent lesion.
    - • Nominal ≥T3 (recurrent lesion ≥4 cm in diameter or minor bone erosion or deep invasion >6 mm measured from the granular layer of normal adjacent epithelium).
    - • Poorly differentiated histology and ≥20 mm diameter of recurrent lesion

The recurrent tumour must be documented to be within the area of the previously resected CSCC by radial measurement of the greatest radius of the final defect, measured from the estimated centre of the original surgical wound.

Table 10 Baseline characteristics of patients in C-POST trial

C-POST – Demographic and Clinical Characteristics of the Patients at Baseline		
	Cemplimab (N=209)	**Placebo (N=206)**
Age		
Median age (range) - yr	71 (33-87)	70.5 (36-95)
≥65 yr – no. (%)	153 (73.2)	141 (68.4)
Gender		
Male sex – no. (%)	174 (83.3)	174 (84.5)
Race – no. (%)†		
Asian	5 (2.4)	8 (3.9)
White	189 (90.4)	189 (91.7)
Other	1 (0.5)	1 (0.5)
Unknown or not reported	14 (6.7)	8 (3.9)
Geographic region – no. (%)		
North America	37 (17.7)	31 (15.0)
Australia / New Zealand	90 (43.1)	90 (43.7)
RoW	82 (39.2)	85 (41.3)
ECOG performance-status-score – no. (%)‡		
0	133 (63.6)	131 (63.6)
1	76 (36.4)	75 (36.4)
Anatomical region of resected high-risk tumour – no. (%)		

C-POST – Demographic and Clinical Characteristics of the Patients at Baseline		
	Cemplimab (N=209)	**Placebo (N=206)**
Head and neck	166 (79.4)	177 (85.9)
Non-head and neck	43 (20.6)	29 (14.1)
High-risk category – no. (%)§		
Nodal	125 (59.8)	117 (56.8)
Non-nodal	84 (40.2)	89 (43.2)
High-risk criteria – no. (%)		
Nodal disease with extracapsular extension and ≥1 lymph node ≥20 mm in diameter	105 (50.2)	96 (46.6)
Nodal disease with ≥3 nodes positive on surgical pathology report, regardless of extracapsular extension	33 (15.8)	37 (18.0)
In-transit metastases	20 (9.6)	21 (10.2)
T4 lesion	17 (8.1)	16 (7.8)
Perineural invasion	32 (15.3)	32 (15.5)
Recurrent high-risk cutaneous squamous-cell carcinoma with ≥1 additional feature	55 (26.3)	50 (24.3)
- ≥N2b disease associated with the recurrent lesion	17 (8.1)	13 (6.3)
- ≥T3 lesion	37 (17.7)	29 (14.1)
- Poorly differentiated histologic findings and diameter of recurrent lesion ≥20 mm	16 (7.7)	13 (6.3)
PD-L1 tumour proportion score — no. (%)		
≥1%	155 (74.2)	154 (74.8)
<1%	42 (20.1)	43 (20.9)
Indeterminate	12 (5.7)	9 (4.4)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The target patient population includes all adults with high risk for recurrence of cutaneous squamous-cell carcinoma after surgery and radiotherapy.

The C-POST study, on this basis, defined high-risk by at least 1 of the following:

a) Nodal disease with (i) ECE and at least 1 node >20 mm on the surgical pathology report, and/or (ii) ≥3 lymph nodes positive on surgical pathology report, regardless of ECE. *ECE is defined as extension through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. Unambiguous evidence of gross ECE (defined as invasion of skin, infiltration of musculature/fixation to adjacent structures on clinical examination) is a sufficiently high threshold to classify these as ECE positive (51).

b) ITM, defined as skin or subcutaneous metastases that are >2 cm from the primary lesion but are not beyond the regional nodal basin (52).

c) T4 lesion, including HN lesions (51) and non-HN lesions. d. PNI, defined as clinical and/or radiologic involvement of named nerves.

d) Recurrent CSCC, defined as CSCC that arises within the area of the previously resected tumour, plus at least 1 of the following additional features (51):

    i. ≥N2b disease associated with the recurrent lesion.

    ii. Nominal ≥T3 (recurrent lesion ≥4 cm in diameter or minor bone erosion or deep invasion >6 mm measured from the granular layer of normal adjacent epithelium).

    iii. Poorly differentiated histology and ≥20 mm diameter of recurrent lesion

In Danish clinical practice (7), CSCC is defined as high-risk when:

g) Tumour size ≥ 2 cm in diameter

h) Location: Lip, ear, perineum, perianal or genital

i) Immunosuppressed patient

j) Recurrence of tumour

k) Tumour occurring in chronically damaged skin such as Marjolins ulcus, osteomyelitis, scars, burns or radiation-damaged skin

l) Histology: Low degree of differentiation, Tumour thickness >2 mm, Invasion into deep dermis or subcutis (Clark level IV and V), Perineural, perivascular or perilymphatic invasion, Tumour depth is related to risk of metastasis.

These guidelines are consistent with European consensus (23) and in some respects broader than of the C-POST study. While the Danish criteria for 'high-risk' CSCC, unlike the criteria used in the C-POST trial, includes some more common risk factors such as tumour size >2cm in diameter and immunosuppression, there are key overlaps between the classifications such as: recurrence of tumour, low degree of differentiation and tumour thickness, perineural invasion.

There is limited information available to precisely define the high-risk CSCC population in Denmark and we expect that the local classification will in most cases capture those deemed high-risk in the C-POST study.

Table 11 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
N/A		

6.1.4 Efficacy – results per C-POST study

The following sections will summarise key efficacy findings obtained from the C-POST study (10), published May 2025. A data cut-off of 04. Oct. 2024 was used, with a median follow-up of 24 months. Efficacy analyses were conducted according to the randomized assignment (intention-to-treat) approach. Data from a later, unpublished data cut-off of 07 April 2025 (DCO2) is also included for the primary and secondary endpoints (53).

6.1.4.1 Statistical Analysis

The C-POST study planned for a total enrolment of 412 patients. Based on literature and the analysis of the POST/TROG 05.01 trial (24), a 3-year disease-free survival of 55% in the placebo group, with a hazard ratio of 0.6 for the comparison of cemiplimab with placebo, was assumed. It was calculated that 165 events of disease recurrence or death (disease-free survival analysis) with three interim analyses (at approximately 83, 107, and 132 events) would provide the trial with 90% power to detect a significant between group difference in disease-free survival at a two-sided alpha of 0.05. Prespecified interim analyses used the Lan–DeMets O'Brien–Fleming spending function to control for the type I error. This publication presents data from the first interim analysis of the fully enrolled trial (data-cutoff date, October 4, 2024). Because this analysis crossed the prespecified efficacy threshold for disease-free survival, it became the primary analysis (10, 11).

Efficacy analyses were conducted according to the randomized assignment (intention-to-treat approach). For the primary efficacy analysis of disease-free survival, hypothesis testing between the two groups was performed with the use of a stratified log-rank test. Hypothesis testing was not performed for secondary end points. For time-to-event analyses, hazard ratios and 95% confidence intervals were estimated with the use of a stratified Cox regression model. The stratification factors for log-rank tests and Cox regression models were tumour location (head and neck vs. non–head and neck) and geographic region (North America vs. Australia or New Zealand vs. the rest of the world). Subgroup analyses of disease-free survival estimated the between-group treatment effect and nominal 95% confidence interval in prespecified subgroups. Safety analyses were based on whether the patient received cemiplimab or placebo and were conducted in all the patients who received any cemiplimab or placebo (10, 11).

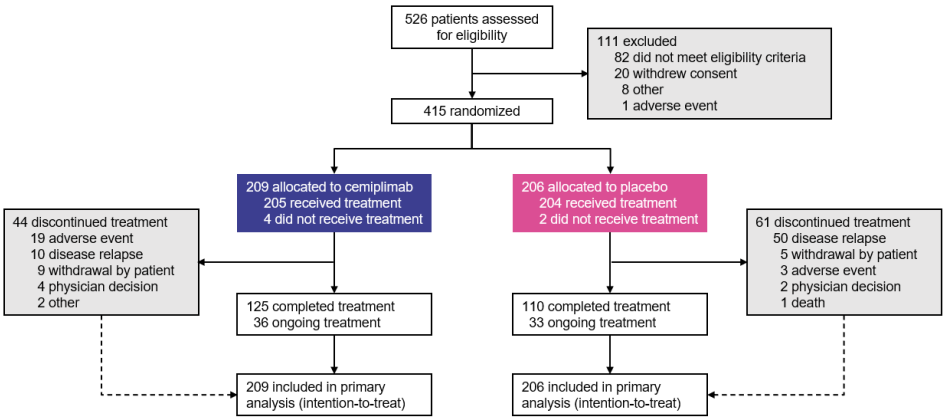
Prespecified analyses of patient-reported outcomes included descriptive analyses and overall changes from baseline across treatment cycles, which were analysed with the use

of a mixed effects model for repeated measures. These analyses were conducted in patients who had a baseline score and at least one post-baseline score for the patient-reported outcome. All the data were analysed with the use of SAS software, version 9.4 (SAS Institute) (10, 11).

6.1.4.2 Patient Disposition

From June 2019 through August 2024, a total of 526 patients at high risk for recurrence of cutaneous squamous-cell carcinoma underwent screening, and 415 were randomly assigned to receive adjuvant therapy with cemiplimab (209 patients) or placebo (206). Among all the patients, the median age was 71 years (range, 33 to 95), 83.9% were men, and 82.7% had primary cutaneous squamous-cell carcinoma of the head and neck. The high-risk nodal disease category included 242 patients (58.3%). The most common high-risk criterion was extra-capsular extension in at least one node measuring at least 20 mm in diameter (in 48.4% of the patients). Overall, the demographic and disease characteristics of the patients at baseline were well balanced between the two trial groups and were generally representative of patients with high-risk cutaneous squamous-cell carcinoma (10).

Figure 3 Patient Disposition, C-POST trial (DCO1, Oct 2024)



Source: C-POST trial (10)

[redacted]

[redacted]

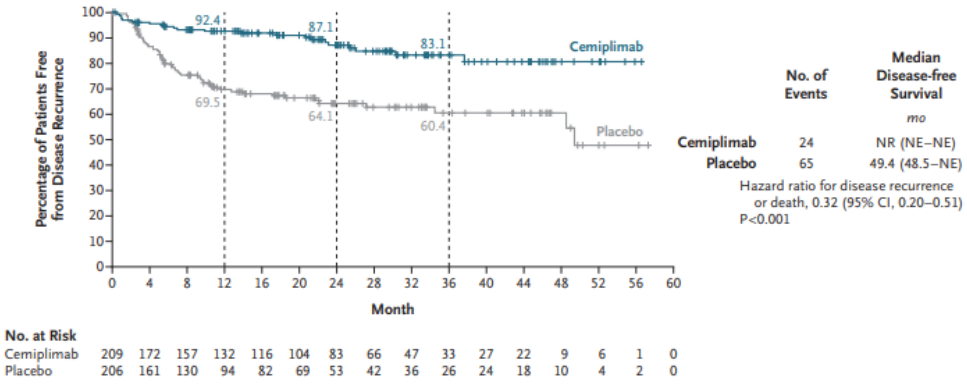
6.1.4.3 Primary efficacy endpoint – Disease-free survival

The primary end point was DFS, defined as the time from randomization to the first documented disease recurrence (locoregional or distant) or death due to any cause. For patients who did not have a tumour recurrence or death, DFS is censored on the date of last disease assessment.

For the study to be declared positive for the primary endpoint of DFS at interim analysis-1 (IA1, DCO 04-10-2024) (10, 11), the significance threshold was set to 0.00455 using the O'Brien-Fleming alpha spending function. If the control arm performed per assumptions in statistical design in the protocol this would correspond to an HR of ≤0.54 based on the actual 89 DFS events at IA1. This study met its primary endpoint of DFS at IA1 (11).

At DCO1 (Oct 2024, Figure 4), a statistically significant and clinically meaningful improvement in disease-free survival was seen in the cemiplimab group as compared with the placebo group (24 vs. 65 events; hazard ratio for disease recurrence or death, 0.32; 95% confidence interval [CI], 0.20 to 0.51; P<0.001) (10). The Kaplan–Meier curves for the analysis of disease-free survival separated early and remained so for the duration of follow-up. The estimated disease-free survival at 24 months was 87.1% (95% CI, 80.3 to 91.6) in the cemiplimab group and 64.1% (95% CI, 55.9 to 71.1) in the placebo group (10).

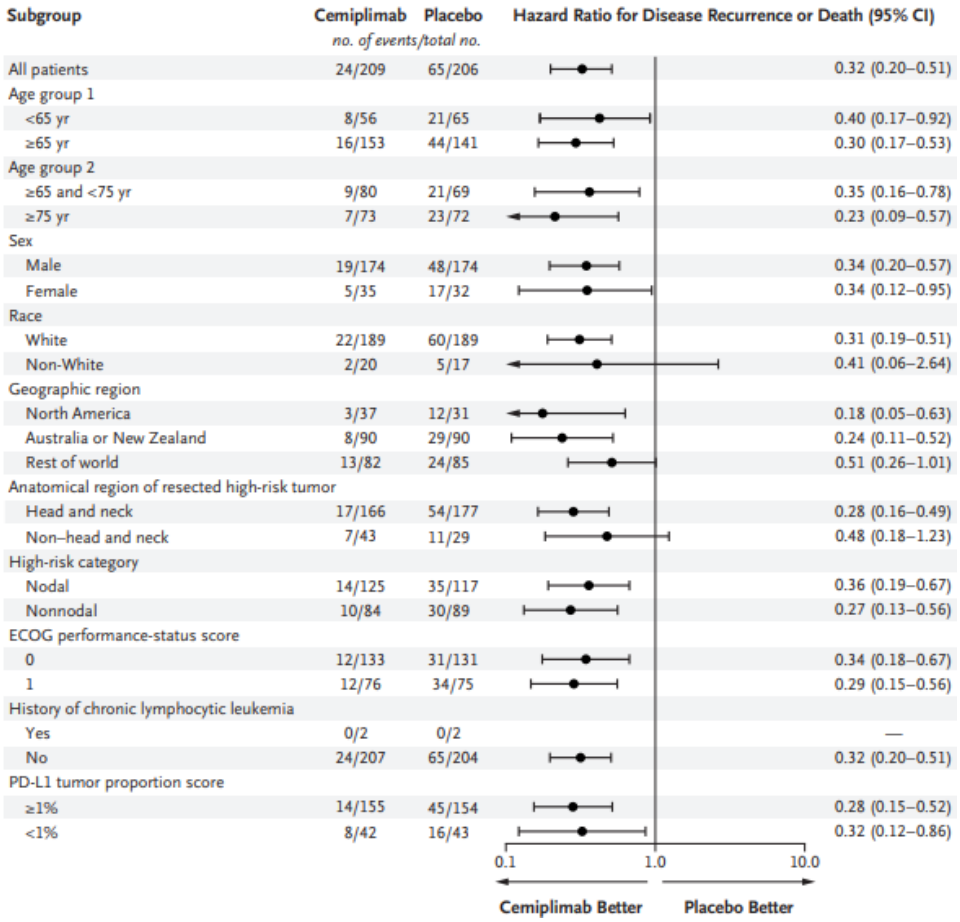
Figure 4 Kaplan-Meier plot of disease-free survival (DCO1, 04 October 2024)



Abbreviations: CI, confidence interval; DCO, data cutoff; NR, not reached; NE, not estimable.
Data cutoff date: 04 October 2024.
Analyses of disease-free survival were based on the Kaplan–Meier method, with stratification according to high-risk tumor (head and neck vs. non–head and neck) and geographic region (North America vs. Australia or New Zealand vs. the rest of the world). The threshold for significance was set to 0.00455 on the basis of the O'Brien–Fleming alpha spending function. The P value was based on a stratified proportional-hazards model. Second primary cutaneous squamous-cell carcinoma tumors were not included as events in the primary end-point analysis of disease-free survival (7).
Source: Rischin et al.(10)

With regard to the 65 events of disease recurrence or death in the placebo group, 61 patients had disease recurrence and 4 died without disease recurrence; with regard to the 24 events in the cemiplimab group, 18 patients had disease recurrence and 6 died without disease recurrence (10). The disease-free survival benefit with cemiplimab in relevant subgroups is shown in Figure 5 D (10).

Figure 5 Disease-free survival according to prespecified subgroups (DCO1, 04 Oct 2024)



Subgroup	Cemiplimab	Placebo	Hazard Ratio for Disease Recurrence or Death (95% CI)
	no. of events/total no.		
All patients	24/209	65/206	0.32 (0.20–0.51)
Age group 1			
<65 yr	8/56	21/65	0.40 (0.17–0.92)
≥65 yr	16/153	44/141	0.30 (0.17–0.53)
Age group 2			
≥65 and <75 yr	9/80	21/69	0.35 (0.16–0.78)
≥75 yr	7/73	23/72	0.23 (0.09–0.57)
Sex			
Male	19/174	48/174	0.34 (0.20–0.57)
Female	5/35	17/32	0.34 (0.12–0.95)
Race			
White	22/189	60/189	0.31 (0.19–0.51)
Non-White	2/20	5/17	0.41 (0.06–2.64)
Geographic region			
North America	3/37	12/31	0.18 (0.05–0.63)
Australia or New Zealand	8/90	29/90	0.24 (0.11–0.52)
Rest of world	13/82	24/85	0.51 (0.26–1.01)
Anatomical region of resected high-risk tumor			
Head and neck	17/166	54/177	0.28 (0.16–0.49)
Non–head and neck	7/43	11/29	0.48 (0.18–1.23)
High-risk category			
Nodal	14/125	35/117	0.36 (0.19–0.67)
Nonnodal	10/84	30/89	0.27 (0.13–0.56)
ECOG performance-status score			
0	12/133	31/131	0.34 (0.18–0.67)
1	12/76	34/75	0.29 (0.15–0.56)
History of chronic lymphocytic leukemia			
Yes	0/2	0/2	—
No	24/207	65/204	0.32 (0.20–0.51)
PD-L1 tumor proportion score			
≥1%	14/155	45/154	0.28 (0.15–0.52)
<1%	8/42	16/43	0.32 (0.12–0.86)

Abbreviations: CI, confidence interval; DCO, data cutoff.
Data cutoff date: 04 October 2024.
Source: Rischin et al.(10)

[redacted] (Figure 6)[redacted].

Figure 6 Kaplan-Meier plot of disease-free survival (DCO2, 07 April 2025)

[redacted]

6.1.4.4 Secondary efficacy endpoint: Freedom from locoregional and distant recurrence

Freedom from locoregional recurrence (FFLRR) is defined as time from randomization to the date of first LRR. Patients who died without a preceding LRR will be censored on the date of death. For patients who did not have a LRR or death, FFLRR will be censored on the date of last disease assessment.

Freedom from distant recurrence (FFDR) is defined as time from randomization to the date of first DR. Patients who died without a preceding DR will be censored on the date of death. For patients who did not have a DR or death, FFDR will be censored on the date of last disease assessment.

Definitions of locoregional recurrence (LRR) and distant recurrence (DR) take into consideration the location of the high-risk CSCC tumour of the individual patient. Definitions are provided in Table 12 for patients in which the high-risk CSCC lesion is in the head and neck (HN) (CSCC, HN) and for patients in which the high-risk CSCC lesion is not in the HN (CSCC, non-HN).

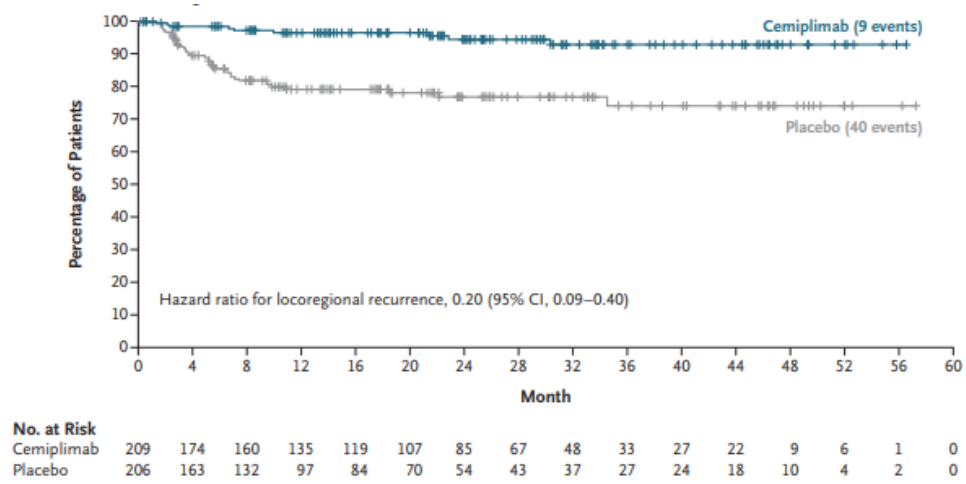
Table 12 Patterns of disease recurrence

Locoregional Recurrence Definitions	Distant Recurrence Definitions
CSCC, HN: Recurrence (nodal or soft tissue) above the clavicle	**CSCC, HN:** Recurrence (nodal) below the clavicle
CSCC, Non-HN: Recurrence (nodal or soft tissue) within the first draining nodal basin (or soft tissue associated within the first draining nodal basin) of the resected tumour	**CSCC, Non-HN:** Recurrence (nodal) beyond the first draining nodal basin of the resected tumour bed
Any tumour (HN or Non-HN): ITM, which are skin or subcutaneous metastases that are >2 cm from the primary lesion but are not beyond the regional nodal basin	**Any tumour (HN or Non-HN):** Recurrence in non-nodal tissue (including, but not limited to, lung, liver, bone, brain, etc). Includes EDM, which are distant lesion(s) in the dermis not originating from epidermis

Abbreviations: CSCC, Cutaneous squamous cell carcinoma; EDM, Epidermotropic metastases; HN, Head and neck; Non-HN, Non-Head and neck; ITM, In-transit metastases

At DCO1, cemiplimab treatment prolonged freedom from both locoregional and distant recurrences as compared with placebo (Figure 7). The estimated percentage of patients free from locoregional recurrence at 24 months was 94.6% (95% CI, 89.1 to 97.3) in the cemiplimab group and 76.7% (95% CI, 69.1 to 82.6) in the placebo group. Locoregional recurrence occurred in 9 patients in the cemiplimab group and in 40 patients in the placebo group (hazard ratio, 0.20; 95% CI, 0.09 to 0.40).

Figure 7 Kaplan-Meier plot of freedom from locoregional recurrence (DCO1, 04 Oct 2024)



Abbreviations: CI, confidence interval; DCO, data cutoff.
Data cutoff date: 04 October 2024.
Source: Rischin et al.(10)

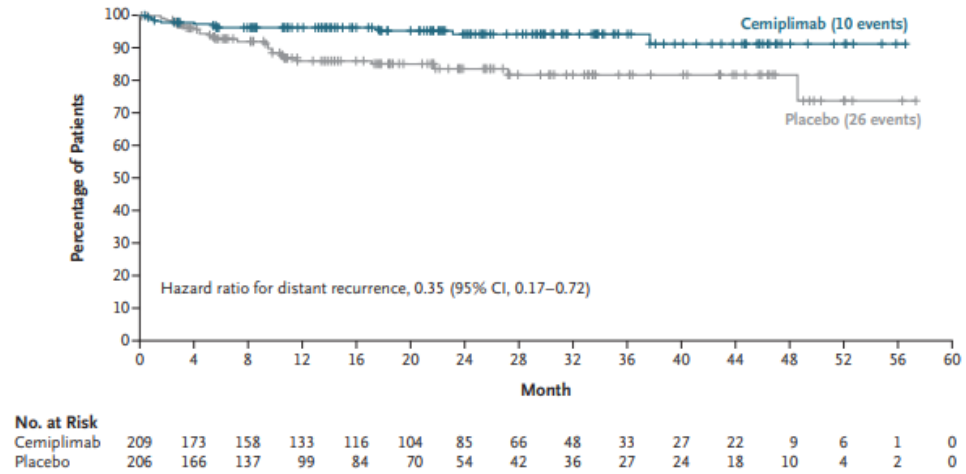
[redacted] (Figure 8) [redacted]

Figure 8 Kaplan-Meier plot of freedom from locoregional recurrence (DCO2, 07 April 2025)

[redacted]

At DCO1 (Oct 2024), the estimated percentage of patients free from distant recurrence at 24 months was 94.3% (95% CI, 89.0 to 97.1) in the cemiplimab group and 83.8% (95% CI, 76.3 to 89.0) in the placebo group (Figure 9) (10). Distant recurrence occurred in 10 patients in the cemiplimab group and in 26 in the placebo group (hazard ratio, 0.35; 95% CI, 0.17 to 0.72) (10).

Figure 9 Kaplan-Meier plot of freedom from distant recurrence (DCO1, 04 Oct 2024)



Abbreviations: CI, confidence interval.
Data cutoff date: 04 October 2024.
Source: Rischin et al.(10)

[redacted] (Figure 10) [redacted]

Figure 10 Kaplan-Meier plot of freedom from distant recurrence (DCO2, 07 April 2025)

[redacted]

Among patients with recurrent disease, the most common subsequent intervention was cemiplimab. Of the 46 patients who had been originally randomly assigned to the placebo group and received cemiplimab for recurrent disease in part 2 of the trial, 20 (43%) had an objective radiographic response (10).

6.1.4.5 Secondary efficacy endpoint: Occurrence of second primary tumours

Occurrence of second primary CSCC tumours (SPTs) is defined as cumulative occurrence of SPTs for each patient from randomization to occurrence of first primary endpoint event or EOS. SPTs are non-metastatic CSCC lesions in the skin that can be managed by local modality therapy as part of routine clinical practice and are not related to the patient's high-risk tumour. SPTs are not DFS events in this study (11).

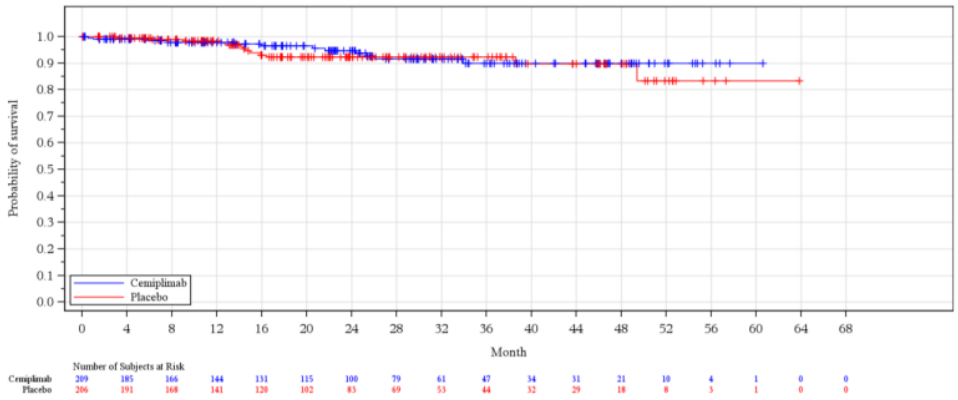
There were 191 Second Primary CSCC Tumours (SPTs), occurring in 68 patients, recorded in the Part 1 study period (period from randomization to EOS, includes on-treatment period and follow-up period; excludes Part 2). Although the number of patients with at least one SPT was similar in both arms (31 patients in the cemiplimab arm and 37 patients in the placebo arm) during the study period, the total number of SPTs was lower in the cemiplimab arm (68 SPTs) than in the placebo arm (123 SPTs) during the study period. The adjusted annualised SPT rate during the study period was 0.633 (95% CI: 0.361, 1.110) for the cemiplimab group and 1.202 (95% CI: 0.592, 2.442) for the placebo group. Thus, the annualised SPT rate ratio for the placebo arm versus the cemiplimab arm during the study period was 1.900 (11). SPTs were also analysed for the treatment period, with the adjusted annualised SPT rate being 1.231 (95% CI: 0.597, 2.539) for the cemiplimab group and 2.812 (95% CI: 1.226, 6.446) for the placebo group. The annualised SPT rate ratio for the placebo arm versus the cemiplimab arm for the treatment period was 2.284 (11). [redacted]

6.1.4.6 Secondary efficacy endpoint: Overall survival

Overall survival is defined as time from randomization to the date of death. A patient who has not died will be censored on the last known date as alive. Hypothesis testing is not performed because 3-year OS in the control arm is expected to be ≥80%, based on result of the POST 05.01 study (24).

A total of 25 deaths had occurred as of DCO1 (Oct 2024, Figure 11): 12 deaths (4 in the cemiplimab group and 8 in the placebo group) were due to disease progression and 13 deaths (8 in the cemiplimab group and 5 in the placebo group) were due to other causes. Overall survival (OS) at 2 years was 94.8% (95% CI, 89.6 to 97.4) in the cemiplimab group and 92.3% (95% CI, 86.5 to 95.7) in the placebo group. The hazard ratio for death was 0.86 (95% CI, 0.39 to 1.90), with 51 patients in the placebo group receiving cemiplimab after recurrence.

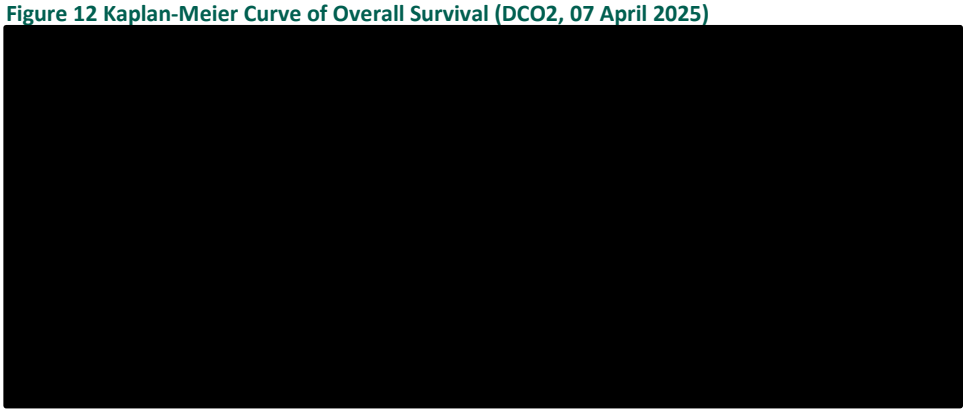
Figure 11 Kaplan-Meier Curve of Overall Survival (DCO1, 04 October 2024)



Data cutoff date: 04 October 2024.
Source: CSR Figure 7 (11)

At a later, unpublished data-cutoff (DCO2, April 2025), there were 33 deaths (15 in the cemiplimab group and 18 in the placebo group), with a hazard ratio of 0.78 (95% CI, 0.39 to 1.56) (Figure 12) (10, 53).

Figure 12 Kaplan-Meier Curve of Overall Survival (DCO2, 07 April 2025)



6.1.4.7 Subsequent therapy for CSCC recurrence

Adjuvant cemiplimab improved DFS and thereby reduced the need for subsequent anti-cancer therapies. At DCO1 (Oct 2024), the most common intervention for recurrent disease was systemic therapy, reported in 51 patients (24.8% [51/206]) randomised to the placebo arm, compared to 10 patients (4.8% [10/209]) randomised to the cemiplimab arm. RT and surgery were less commonly used as management for recurrence disease, compared to systemic therapy. Higher percentages of patients randomised to placebo, versus cemiplimab, required subsequent RT (3.4% [7/206] versus 2.4% [5/209]) and subsequent surgery (5.3% [11/206] versus 1.9% [4/209]). Subsequent management of patients who experienced disease recurrences is summarised in Table 13.

Table 13 Subsequent therapy for CSCC recurrence (Full Analysis Set) – Part 1

	Cemiplimab (N=209)	Placebo (N=206)
No. participants with recurrence, n (%) [a]	18 (8.6)	61 (29.6)
No. participants who received systemic therapy, n (%)	10 (4.8) [b]	51 (24.8) [c]
Cemiplimab, n (%)	5 (2.4) [d]	51 (24.8) [e]
Other, n (%)	6 (2.9) [f]	6 (2.9) [g]
No. participants who received RT, n (%)	5 (2.4)	7 (3.4)
No. participants who had surgery, n (%)	4 (1.9)	11 (5.3)

Data cutoff date: 04 October 2024
Source: Regeneron data on file, C-POST CSR (11)

Abbreviations: No., number of; RT, radiotherapy
[a] The total number of recurrences is provided in this row. The number of interventions (systemic therapy, surgery, radiation) for recurrent CSCC in the rows below sums to more than the total number of recurrences, because some patients received more than 1 intervention for recurrent CSCC. [b] The top row indicates 10 patients received systemic therapy for recurrent disease. The indented rows below sum to 11 because 1 patient received cemiplimab and another line of 5-Fluorouracil (5FU). [c] The top row indicates 51 patients received systemic therapy for recurrent disease. The indented rows below sum to 57 because several patients received more than 1 line of systemic therapy. [d] This includes 3 patients who received in Part 2 and 2 patients who received cemiplimab outside of Part 2 for recurrent disease as part of standard of care. [e] This includes 46 patients who received cemiplimab in Part 2 and 5 patients who received cemiplimab outside of Part 2 for recurrent disease as part of standard of care. 2 patients who received cemiplimab both in Part 2 and outside of Part 2 are counted as having received cemiplimab in Part 2. [f] The following systemic therapies were reported in the cemiplimab arm in 6 patients: 5-FU single agent (n=1), carboplatin + paclitaxel (n=1), 5-FU + cisplatin (n=1), protein kinase inhibitor (n=1), cetuximab single agent (n=1) and 1 patient received 3 lines of therapy (cetuximab + paclitaxel and cetuximab + docetaxel twice). [g] The following systemic therapies were reported in the placebo arm in 6 patients: carboplatin + paclitaxel (n=2), cetuximab single agent (n=2), carboplatin + 5-FU + cetuximab single agent (n=1) and 1 patient received 2 lines of chemotherapy (cisplatin + 5-FU and carboplatin single agent). Note that 1 patient received cemiplimab twice (in Part 2 and as standard of care) and carboplatin + paclitaxel

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Head-to-head study used. Not applicable.

7.1.2 Method of synthesis

Head-to-head study used. Not applicable.

7.1.3 Results from the comparative analysis

Table 14 Results from the comparative analysis of adjuvant cemiplimab vs. placebo for CSCC patients at high risk of recurrence after surgery and radiotherapy, DCO1 04 Oct 2025

Outcome measure	Cemiplimab (N=209)	Placebo (N=206)	Result
Median DFS by Oct 4, 2024, months (95% CI)	NR (NE,NE)	49.4 (48.5, NE)	HR: 0.32 (95% CI: 0.20, 0.51; P<0.0001) [a][b]
No. DFS events by Oct 4, 2024, n (%)	24 (11.5%)	65 (31.6%)	NA
Estimated DFS by 04 Oct 2024, % (95% CI) [d]			
12 months	92.4 (87.5, 95.5)	69.5 (62.1, 75.7)	NA

Outcome measure	Cemiplimab (N=209)	Placebo (N=206)	Result
24 months	87.1 (80.3, 91.6)	64.1 (55.9, 71.1)	NA
36 months	83.1 (74.9, 88.9)	60.4 (51.1, 68.5)	NA
Median FFLRR by Oct 4, 2024, months (95% CI)	NR (NE, NE)	NR (NE, NE)	HR: 0.20 (95% CI: 0.09, 0.40) [a][b]
No. LRR events by Oct 4, 2024, n (%)	9 (4.3%)	40 (19.4%)	NA
Median FFDR by Oct 4, 2024, months (95% CI)	NR (NE, NE)	NR (NE, NE)	HR: 0.35 (95% CI: 0.17, 0.72)
No. DR events by Oct 4, 2024, n (%)	10 (4.8%)	26 (12.6%)	NA
No. Patients with at least 1 SPT by Oct 4. 2024, n (%)	31 (14.8%)	37 (18%)	NA
Deaths by Oct 4, 2024, n (%)	12 (5.7%)	13 (6.3%)	NA
OS Median by Oct 4, 2024 (95% CI) [c]	NR (NE, NE)	NR (NE, NE)	HR: 0.86 (95 % CI: 0,39, 1.90) [a][b]
Estimated Survival Probability by 04 Oct 2024 [d]**, % (95% CI)**			NA
6 months	98.5 (95.3, 99.5)	99.5 (96.4, 99.9)	NA
12 months	97.9 (94.4, 99.2)	98.3 (94.8, 99.5)	NA
24 months	94.8 (89.6, 97.4)	92.3 (86.5, 95.7)	NA
36 months	89.9 (82.1, 94.4)	92.3 (86.5, 95.7)	NA

[a] Stratified by high-risk tumour location (HN versus non-HN) and geographical region (North America versus Australia/New Zealand versus ROW) per EDC. [b] Based on stratified proportional hazards model (cemiplimab versus placebo). [c] Median overall survival not yet reached for neither cemiplimab nor placebo groups. [d] Based on Kaplan-Meier method.

Abbreviations: CI, Confidence interval; DR, distant recurrence; EDC, Electronic data capture (database); FFDR, freedom from distant recurrence; FFLRR, freedom from locoregional recurrence; LRR, locoregional recurrence; HN, Head and neck; HR, Hazard ratio; NE, Not established; NR, Not reached; ROW, Rest of world.

Source: Rischin et al (10), CSR (11)

Table 15 Results from the comparative analysis of adjuvant cemiplimab vs. placebo for CSCC patients at high risk of recurrence after surgery and radiotherapy, DCO2 07 April 2025

Outcome measure	Cemiplimab (N=209)	Placebo (N=206)	Result
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[a] Stratified by high-risk tumour location (HN versus non-HN) and geographical region (North America versus Australia/New Zealand versus ROW) per EDC. [b] Based on stratified proportional hazards model (cemiplimab versus placebo). [c] Median overall survival not yet reached for neither cemiplimab nor placebo groups.[d] Based on Kaplan-Meier method.
Abbreviations: CI, Confidence interval; DR, distant recurrence; EDC, Electronic data capture (database); FFDR, freedom from distant recurrence; FFLRR, freedom from locoregional recurrence; LRR, locoregional recurrence; HN, Head and neck; HR, Hazard ratio; NE, Not established; NR, Not reached; ROW, Rest of world.
Source: Regeneron data on file, DCO2 (53)

7.1.4 Efficacy – results per [outcome measure]

Results per efficacy outcome are summarized in section 6. Results in relation to health-related quality of life are summarized in section 10.

8. Modelling of efficacy in the health economic analysis

8.1 N/A – this section is not applicable as cemiplimab is a PD-1 inhibitor, per the DMC process guide for 14-week submissions. Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

Not applicable

8.1.1.1 Extrapolation of [effect measure 1]

Table 16 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	Not applicable

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable

8.1.2 Calculation of transition probabilities

Table 17 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence	Not applicable	
	Death		
Recurrence	Death		
Health state/Transition			

8.2 Presentation of efficacy data from [additional documentation]

Not applicable

8.3 Modelling effects of subsequent treatments

Not applicable

8.4 Other assumptions regarding efficacy in the model

Not applicable

8.5 Overview of modelled average treatment length and time in model health state

Not applicable

Table 18 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	Not applicable		

Table 19 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
[Intervention]	Not applicable		

9. Safety

9.1 Safety data from the clinical documentation

The safety data is derived from the C-POST head-to-head trial, with data presented from the DCO1 date of 04 Oct 2024. Unpublished data from the DCO2 data of 07 April 2025 (53) is included only in table format (Table 21, Table 23) due to the similarities of the data between DCO1 and DCO2. The safety analysis set (SAF) consists of all C-POST 409 patients who underwent randomization and received at least one dose of cemiplimab or placebo. The following definitions are used (11):

On-treatment period: the time from first dose of study treatment to last dose of study treatment plus 90 days, or to 1 day before patients receive their first cemiplimab dose in Part 2 of the study (subsequent cemiplimab treatment) or another anti-cancer systemic therapy, whichever is earlier.

Post-treatment period: the time starting 1 day after the end of on-treatment period.

Treatment-emergent adverse events (TEAEs): defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occur during the post-treatment period but prior to Part 2 of the study (subsequent cemiplimab treatment).

The median duration of exposure by DCO1 was 47.9 weeks (range, 3 to 52) in the cemiplimab group (N=205) and 47.7 weeks (range, 3 to 51) in the placebo group (N=204). Overall, the median potential follow-up from randomization to the data-cutoff date was 24 months (range, 2 to 64). As of the data-cutoff date, 69 patients (16.9%; 36 in the cemiplimab group and 33 in the placebo group) were still receiving cemiplimab or placebo in part 1 of the trial (10, 11).

Overall, 44 of 205 patients receiving cemiplimab (21.5%) and 61 of 204 patients receiving placebo (29.9%) discontinued the regimen during part 1 of the trial. In the cemiplimab group, the most common reasons for discontinuation were adverse events (in 19 patients), disease relapse (in 10), and patient decision to withdraw (in 9); in the placebo group, the most common reasons were disease relapse (in 50) and patient decision to withdraw (in 5) (10, 11).

Adverse events of any cause during the treatment period occurred in 91.2% of the patients who received cemiplimab and in 89.2% of those who received placebo (Table 20). The most common adverse events with cemiplimab as compared with placebo were fatigue (in 22.0% vs. 21.6% of the patients), pruritus (in 16.1% vs. 12.3%), rash (in 16.1% vs. 8.8%), and diarrhoea (in 15.6% vs. 18.6%). Adverse events of grade 3 or higher that were due to any cause occurred in 23.9% of the patients who received cemiplimab and in 14.2% of those who received placebo.

Cemiplimab or placebo was discontinued owing to adverse events in 9.8% and 1.5% of the patients, respectively. Immune-related adverse events occurred in 22.9% of the patients who received cemiplimab (with events of grade ≥3 in 7.3%) and in 6.4% of those who

received placebo (with no events of grade ≥3). No unexpected immune-related adverse events were observed (10, 11). The safety profile of cemiplimab in the adjuvant setting in the C-POST study is consistent with the known safety profile for cemiplimab monotherapy in advanced cancers.

Table 20 Overview of safety events DCO1, 04 Oct 2024

	Cemiplimab (N=205) (10, 11)	Placebo (N=204) (10, 11)
Number of adverse events, n	NA	NA
Number and proportion of patients with ≥1 adverse events, n (%)	187 (91.2)	182 (89.2)
Number of serious adverse events*, n	NA	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	36 (17.6)	19 (9.3)
Number of CTCAE grade ≥ 3 events, n	NA	NA
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	49 (23.9)	29 (14.2)
Number of adverse reactions, n	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	128 (62.4)	94 (46.1)
Number and proportion of patients who had a dose reduction, n (%)	NA	NA
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	44 (21.1)	61 (29.6)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	20 (9.8)	3 (1.5)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
§ CTCAE v. 5.0 must be used if available.
Source: C-POST (10, 11)

Table 21 Overview of safety events DCO2, 07 Apr 2025

	Cemiplimab (N=205)	Placebo (N=204)
Number of adverse events, n	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]
Number of serious adverse events*, n	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	[redacted]	[redacted]
Number of adverse reactions, n	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
§ CTCAE v. 5.0 must be used if available.
Source: Regeneron DCO2 data on file (53)

No serious adverse events were reported to affect more than 5% of either arm, as shown in Table 22 (11). Remaining SAEs are reported in Appendix E.

Table 22 Serious adverse events affecting over 5% of either arm, DCO1 04 Oct 2024

Adverse events	Cemiplimab (N=205)		Placebo (N=204)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Overall, n (%)	36 (17.6)	N/A	19 (9.3)	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Source: C-POST CSR (11)

Table 23 Serious adverse events affecting over 5% of either arm, DCO2 07 Apr 2025

Adverse events	Cemiplimab (N=205)		Placebo (N=204)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Overall, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Source: C-POST DCO2 TFLs (53)

Table 24 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for	Frequency used in economic model for	Source	Justification

Adverse events	Intervention	Comparator
	intervention	comparator
Adverse event, n (%)	N/A	

9.2 Safety data from external literature applied in the health economic model

Not applicable

Table 25 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	Not applicable							

10. Documentation of health-related quality of life (HRQoL)

Table 26 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	C-POST trial	To compare the HRQoL of high-risk CSCC patients treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT
EQ-5D-3L VAS	C-POST trial	To compare the HRQoL of high-risk CSCC patients treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT

Abbreviations: CSCC, cutaneous squamous cell carcinoma; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L, the EuroQOL Five Dimensions Questionnaire 3L Visual Analog Scale; HRQoL, Health-related quality of life; RT, radiotherapy.

10.1 Presentation of the health-related quality of life

10.1.1 EORTC QLQ-C30

10.1.1.1 Study design and measuring instrument

The EORTC QLQ-C30 global health status (GHS)/quality-of-life (QoL) scale and the EQ-5D-3L visual analogue scale (VAS) data from the C-POST trial can provide useful information on the risk–benefit assessment of adjuvant cemiplimab in CSCC. CSCC is primarily a disease of the elderly, underscoring the relevance and importance of preserving QoL in this population. Scoring and interpretation of PRO scales followed respective instrument scoring manuals. The EORTC QLQ-C30 uses a recall period of the “past week.” It includes one GHS/QoL scale, 5 functional scales, 3 symptom scales, and 6 single items (among those 1 financial impact item). Each scale is scored between 0 and 100, with higher scores indicating better QoL/function (for the GHS/QoL and functional scales), but worse/more symptoms (for the symptom scales). The commonly referenced threshold of 10-points was used for interpreting differences between treatment groups as well as interpreting changes within each treatment arm (11).

Pre-specified analyses included (11):

- Descriptive analyses,

- Overall changes from baseline across treatment cycles using mixed effects models for repeated measures (MMRM),
- PRO responder analysis (which categorizes patients into meaningful improvement, maintenance or worsening of their PRO scores from baseline) at each cycle using a published threshold of 10 points for a meaningful change in the EORTC QLQ-C30 GHS/QoL scale,
- Median time to first deterioration, using the same meaningful within-person change thresholds for deterioration (10 points for the EORTC QLQ-C30 GHS/QoL scale) using Kaplan-Meier analyses.

10.1.1.2 Data collection

The EORTC QLQ-C30 and EQ-5D-3L were electronically administered prior to infusion at baseline (day 1 of Cycle 1) and subsequent visits of new treatment cycles (day 1 of cycles 2 through 4). All patients who completed the planned 4 cycles of assigned study treatment without recurrence returned for an end of treatment (EOT) visit and then continued post treatment follow-up visits until disease recurrence to assure that data for the primary endpoint of the study was captured. Analyses focused on the PRO data collected in Part 1 (blinded) of the study only, since in Part 2 (unblinded) of the study, patients were not randomized anymore, hence, PRO data were not collected to minimize patient burden (54).

Completion rates were high at baseline (92.3% for cemiplimab; 93.6% for placebo), remaining above 88% through all regular cycle timepoints (i.e., Cycles 2, 3, 4) across both arms (54).

Table 27 Pattern of missing data and completion

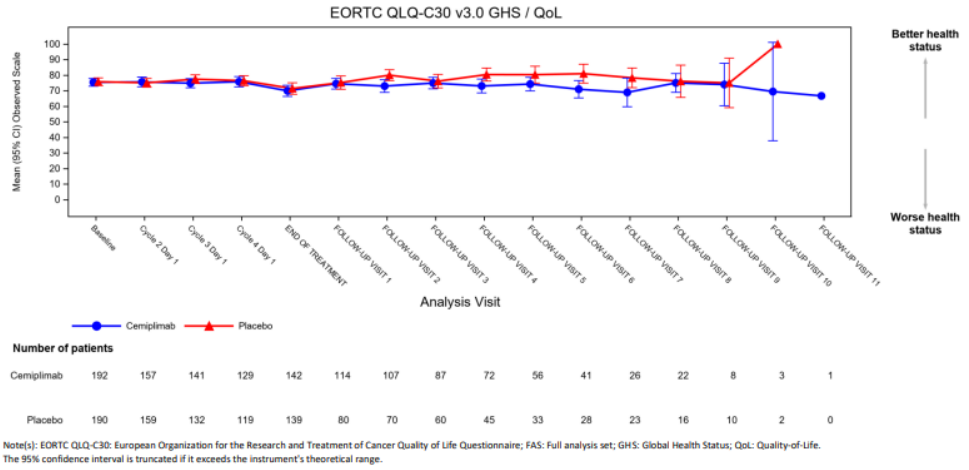
Time point	HRQoL population, N		Missing %		Expected to complete, N		Completion N (%)	
	Cemiplimab	Placebo	Cemiplimab	Placebo	Cemiplimab	Placebo	Cemiplimab	Placebo
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
Baseline	209	206	17 (8)	16 (8)	208	203	192 (92.3)	190 (93.6)
Cycle 2 Day 1	209	206	52 (25)	47 (23)	175	179	157 (89.7)	159 (88.8)
Cycle 3 Day 1	209	206	68 (33)	74 (36)	155	146	141 (91.0)	132 (90.4)
Cycle 4 Day 1	209	206	80 (38)	87 (42)	138	123	129 (93.5)	119 (96.7)
End of treatment	209	206	67 (32)	67 (33)	NA	NA	NA	NA
Follow-up 1	209	206	95 (45)	126 (61)	NA	NA	NA	NA
Follow-up 2	209	206	102 (49)	136 (66)	NA	NA	NA	NA

Time point	HRQoL population, N		Missing %		Expected to complete, N		Completion N (%)	
	Cemiplimab	Placebo	Cemiplimab	Placebo	Cemiplimab	Placebo	Cemiplimab	Placebo
Follow-up 3	209	206	122 (58)	146 (71)	NA	NA	NA	NA
Follow-up 4	209	206	137 (66)	161 (78)	NA	NA	NA	NA
Follow-up 5	209	206	153 (73)	173 (84)	NA	NA	NA	NA
Follow-up 6	209	206	168 (80)	178 (86)	NA	NA	NA	NA
Follow-up 7	209	206	183 (88)	183 (89)	NA	NA	NA	NA
Follow-up 8	209	206	187 (89)	190 (92)	NA	NA	NA	NA
Follow-up 9	209	206	201 (96)	196 (95)	NA	NA	NA	NA
Follow-up 10	209	206	206 (99)	204 (99)	NA	NA	NA	NA
Follow-up 11	209	206	208 (100)	206 (100)	NA	NA	NA	NA

10.1.1.3 HRQoL results

As summarized in Table 28, baseline scores were similar between arms. Overall, least square mean changes from baseline through all treatment cycles on the EORTC QLQ-C30 GHS/QoL were small and similar between arms suggesting preservation of QoL while on treatment. For the EORTC QLQ-C30 GHS/QoL scale, the least square mean changes (standard error) within each treatment arm (-1.95 (1.18) with cemiplimab, -1.02 (1.22) with placebo) and the differences in change between the treatment arms (-0.94 [-3.65, 1.77]), were much smaller than the thresholds for meaningful change (10 points for EORTC QLQ-C30 GHS/QoL scale). Figure 13 shows the mean scores at each treatment cycle and follow-up visit. The maintenance of QoL appears to be sustained following end of treatment.

Figure 13 Mean score over time – EORTC QLQ-C30 GHS/QoL scale



Note(s): EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FAS: Full analysis set; GHS: Global Health Status; QoL: Quality-of-Life. The 95% confidence interval is truncated if it exceeds the instrument's theoretical range.

Source: C-POST CSR (11)

In the PRO responder analysis, most patients in both arms reported maintenance or meaningful improvement in the EORTC QLQ-C30 GHS/QoL scores across all cycles during and following treatment where N≥10 (cemiplimab: 66.0% to 90.0%; placebo: 66.6% to 86.7%). Median time to first deterioration (95% CI; excluding death) for the EORTC QLQ-C30 GHS/QoL scale was similar between arms (cemiplimab: 13.83 [8.48, 25.30]; placebo: 18.60 [8.41, 45.83]).

Table 28 HRQoL EORTC QLQ-C30 GHS/QoL summary statistics

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

	Cemiplimab		Placebo		Cemiplimab vs. Placebo	
EORTC QLQ-C30 GHS/QoL	75.39 (17.48)	-1.95 (1.18), [-4,27, 0.36]	75.75 (17.44)	-1.02 (1.22), [-3.42, 1.39]	-0.83	-0.94 [-3.65, 1.77]

[a] N is the number of subjects with a baseline and at least one post-baseline PRO score. [b] Estimates are based on a mixed model repeated measures treating time categorical: Change=Treatment arm + Time + Baseline PRO Value + Anatomic region of resected high-risk tumour + Geographical region+ Time*Baseline PRO Value +Time point*Treatment arm.
Abbreviations: CI, Confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LS, Least-squares; PRO, Patient reported outcome; QoL, Quality-of-Life; SD, Standard deviation; SE, Standard error
Source: C-POST CSR (11)

10.1.2 EQ-5D-3L

10.1.2.1 Study design and measuring instrument

The EORTC QLQ-C30 global health status (GHS)/quality-of-life (QoL) scale and the EQ-5D-3L visual analog scale (VAS) data from the C-POST trial can provide useful information on the risk–benefit assessment of adjuvant cemiplimab in CSCC. CSCC is primarily a disease of the elderly, underscoring the relevance and importance of preserving QoL in this population. Scoring and interpretation of PRO scales followed respective instrument scoring manuals. Higher scores on the EORTC QLQ-C30 GHS/QoL scale and the EQ-5D-3L VAS indicated better health status.

Pre-specified analyses included:

- Descriptive analyses,
- Overall changes from baseline across treatment cycles using mixed effects models for repeated measures (MMRM),
- PRO responder analysis (which categorizes patients into meaningful improvement, maintenance or worsening of their PRO scores from baseline) at each cycle using a published threshold of 7 points for a meaningful change in the EQ-5D-3L VAS scale,
- Median time to first deterioration, using the same meaningful within-person change thresholds for deterioration (7 points for the EQ-5D-3L VAS scale) using Kaplan-Meier analyses.

10.1.2.2 Data collection

The EORTC QLQ-C30 and EQ-5D-3L were electronically administered prior to infusion at baseline (day 1 of Cycle 1) and subsequent visits of new treatment cycles (day 1 of cycles 2 through 4). All patients who completed the planned 4 cycles of assigned study treatment without recurrence returned for an end of treatment (EOT) visit, and then continued post

treatment follow-up visits every 4 months and every 6 months after year 3 until disease recurrence to assure that data for the primary endpoint of the study was captured. Analyses focused on the PRO data collected in Part 1 (blinded) of the study only, since in Part 2 (unblinded) of the study, patients were not randomized anymore, hence, PRO data were not collected to minimize patient burden (54).

Completion rate was high at baseline (88.9% for cemiplimab; 91.1% for placebo), remaining above 80% through all regular cycle timepoints (i.e., Cycles 2, 3, 4) across both arms.

Table 29 Pattern of missing data and completion

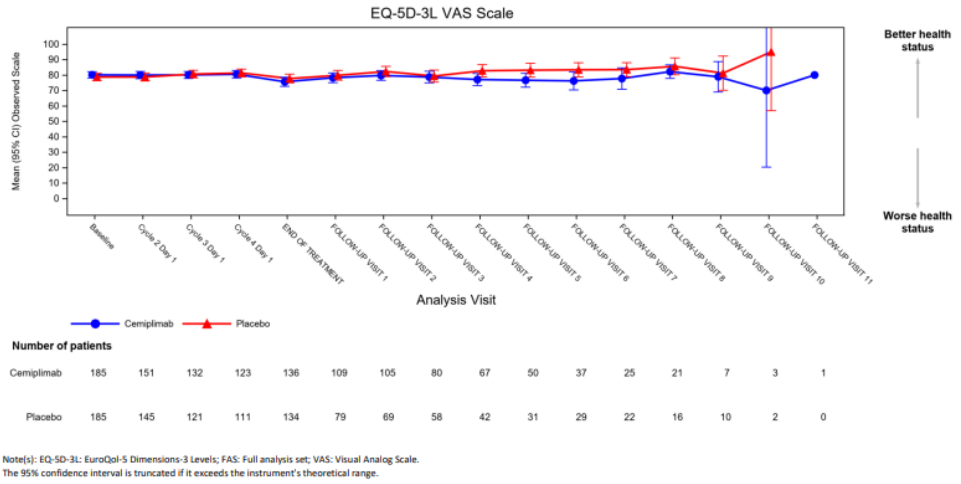
Time point	HRQoL population, N		Missing %		Expected to complete, N		Completion N (%)	
	Cemiplimab	Placebo	Cemiplimab	Placebo	Cemiplimab	Placebo	Cemiplimab	Placebo
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
Baseline	209	206	24 (11)	21 (10)	208	203	185 (88.9)	185 (91.1)
Cycle 2 Day 1	209	206	58 (28)	61 (30)	175	179	151 (86.3)	145 (81.0)
Cycle 3 Day 1	209	206	77 (37)	85 (41)	155	146	132 (85.2)	121 (82.9)
Cycle 4 Day 1	209	206	86 (41)	95 (46)	138	123	123 (89.1)	111 (90.2)
End of treatment	209	206	73 (35)	72 (35)	NA	NA	NA	NA
Follow-up 1	209	206	100 (48)	127 (62)	NA	NA	NA	NA
Follow-up 2	209	206	104 (50)	137 (67)	NA	NA	NA	NA

Time point	HRQoL population, N		Missing %		Expected to complete, N		Completion N (%)	
	Cemiplimab	Placebo	Cemiplimab	Placebo	Cemiplimab	Placebo	Cemiplimab	Placebo
Follow-up 3	209	206	129 (62)	148 (72)	NA	NA	NA	NA
Follow-up 4	209	206	142 (68)	164 (80)	NA	NA	NA	NA
Follow-up 5	209	206	159 (76)	175 (85)	NA	NA	NA	NA
Follow-up 6	209	206	172 (82)	177 (86)	NA	NA	NA	NA
Follow-up 7	209	206	184 (88)	184 (89)	NA	NA	NA	NA
Follow-up 8	209	206	188 (90)	190 (92)	NA	NA	NA	NA
Follow-up 9	209	206	202 (97)	196 (95)	NA	NA	NA	NA
Follow-up 10	209	206	206 (99)	204 (99)	NA	NA	NA	NA
Follow-up 11	209	206	208 (100)	206 (100)	NA	NA	NA	NA

10.1.2.3 HRQoL results

As summarized in Table 30, baseline scores were similar between arms. Overall, least square mean changes from baseline through all treatment cycles on the EQ-5D-3L VAS were small and similar between arms suggesting preservation of QoL while on treatment. For the EQ-5D-3L, the least square mean changes (standard error) within each treatment arm (0.16 (1.03) with cemiplimab, 0.61 (1.07) with placebo) and the differences in change between the treatment arms (-0.45 [-2.85, 1.94]), were much smaller than the thresholds for meaningful change (7 points for the EQ-5D-3L VAS scale). Figure 14 shows the mean scores at each treatment cycle and follow-up visit. The maintenance of QoL appears to be sustained following end of treatment.

Figure 14 Mean score over time, EQ-5D-3L VAS scale



Note(s): EQ-5D-3L: EuroQol-5 Dimensions-3 Levels; FAS: Full analysis set; VAS: Visual Analog Scale.
The 95% confidence interval is truncated if it exceeds the instrument's theoretical range.

Table 30 HRQoL EQ-5D-3L VAS summary statistics

	Cemiplimab		Placebo		Cemiplimab vs. Placebo	
	Baseline Score (observed) : Mean (SD) N=164[a]	Change from baseline : LS Mean (SE) [95% CI]	Baseline Score (observed) : Mean (SD) N=163[a]	Change from baseline : LS Mean (SE) [95% CI]	Observed difference in LS Mean Change	Difference in LS Mean Change [b] [95% CI]
EQ-5D-3L VAS	80.13 (13.96)	0.16 (1.03), [-1.86, 2.18]	78.71 (16.43)	0.61 (1.07), [-1.51, 2.72]	-0.65	-0.45 [-2.85, 1.94]

[a] N is the number of subjects with a baseline and at least one post-baseline PRO score. [b] Estimates are based on a mixed model repeated measures treating time categorical: Change=Treatment arm + Time +

Baseline PRO Value + Anatomic region of resected high-risk tumour + Geographical region+ Time*Baseline PRO Value +Time point*Treatment arm.
Abbreviations: CI, Confidence interval; VAS, Visual analog scale; LS, Least-squares; PRO, Patient reported outcome; QoL, Quality-of-Life; SD, Standard deviation; SE, Standard error
Source: CSR (11)

10.2 Health state utility values (HSUVs) used in the health economic model

N/A – this section is not applicable as cemiplimab is a PD-1 inhibitor, per the DMC process guide for 14-week submissions.

10.2.1 HSUV calculation

Not applicable

10.2.1.1 Mapping

Not applicable

10.2.2 Disutility calculation

Not applicable

10.2.3 HSUV results

Not applicable

Table 31 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

N/A – this section is not applicable as cemiplimab is a PD-1 inhibitor, per the DMC process guide for 14-week submissions.

10.3.2 Data collection

Not applicable

10.3.3 HRQoL Results

Not applicable

10.3.4 HSUV and disutility results

Not applicable

Table 32 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

Table 33 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

N/A – this section is not applicable as cemiplimab is a PD-1 inhibitor, per the DMC process guide for 14-week submissions.

Table 34 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	Not applicable			

11.2 Medicines– co-administration

Not applicable

11.3 Administration costs

Not applicable

Table 35 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
[E.g. i.v. infusion, subcutaneous infusion]	Not applicable			

11.4 Disease management costs

Not applicable

Table 36 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
[Activity]	Not applicable	Not applicable	Not applicable	Not applicable

11.5 Costs associated with management of adverse events

Not applicable

Table 37 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
[Adverse event]	Not applicable	

11.6 Subsequent treatment costs

Not applicable

Table 38 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	Not applicable	Not applicable	Not applicable	Not applicable

11.7 Patient costs

Not applicable

Table 39 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Activity	Not applicable

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable

12. Results

12.1 Base case overview

N/A – this section is not applicable as cemiplimab is a PD-1 inhibitor, per the DMC process guide for 14-week submissions.

Table 40 Base case overview

Feature	Description
Comparator	Not applicable

12.1.1 Base case results

Not applicable

Table 41 Base case results, discounted estimates

	[Intervention]	[Comparator]	Difference
Medicine costs		Not applicable	
Total QALYs			
Incremental costs per life year gained			
Incremental cost per QALY gained (ICER)			

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Not applicable

Table 42 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case		Not applicable			

Not applicable

12.2.2 Probabilistic sensitivity analyses

Not applicable

13. Budget impact analysis

N/A – this section is not applicable as cemiplimab is a PD-1 inhibitor, per the DMC process guide for 14-week submissions.

Number of patients (including assumptions of market share)

Table 43 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
[Name of intervention]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Budget impact

Table 44 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

14. List of experts

N/A

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Appendix A. Main characteristics of studies included

Table 45 Main characteristic of studies included

Trial name: C-POST	**NCT number: NCT03969004**
Objective	The primary objective of the study is to compare DFS of patients with high-risk CSCC treated with adjuvant cemiplimab, versus those treated with placebo, after surgery and RT.
Publications – title, author, journal, year	Adjuvant Cemiplimab or Placebo in High-Risk Cutaneous Squamous-Cell Carcinoma. D. Rischin, S. Porceddu, F. Day, P. Brungs Daniel, H. Christie, E. Jackson James, et al. New England Journal of Medicine 2025 Vol. 393 Issue 8 Pages 774-785 DOI: 10.1056/NEJMoa2502449 (10)
Study type and design	Ongoing, randomized, double-blind, placebo-controlled phase 3 study. All patients were centrally assigned/randomized 1:1 to investigational intervention using an interactive voice response system/interactive web response system and stratified randomisation scheme(11). Part 2 of the study allowed optional subsequent cemiplimab treatment for patients experiencing disease recurrence, with unblinding taking place in these cases unless the patient has experienced disease recurrence after completing the assigned 48 weeks of part 1 study treatment plus over 3 months of follow-up.
Sample size (n)	415
Main inclusion criteria (all must apply)	• Men and women aged ≥18 years (for Japan only, men and women aged ≥21 years) • Patient with resection of pathologically confirmed CSCC (primary CSCC lesion only, or primary CSCC with nodal involvement, or CSCC nodal metastasis with known primary CSCC lesion previously treated within the draining lymph node echelon), with macroscopic gross resection of all disease • High-risk CSCC, defined as ≥1 of the following: • Nodal disease with extracapsular extension and at least 1 node ≥20 mm on the surgical pathology report, and/or ≥3 lymph nodes positive on surgical pathology report, regardless of extracapsular extension

Trial name: C-POST		NCT number: NCT03969004
	• In-transit metastasis (ie, skin or subcutaneous metastases that are >2 cm from the primary lesion but are not beyond the regional nodal basin) • T4 lesion, including HN and non-HN lesions • Perineural invasion, defined as clinical and/or radiologic involvement of named nerves • Recurrent CSCC, defined as CSCC that arises within the area of the previously resected tumour, plus at least 1 of the following additional features: ≥N2b disease associated with the recurrent lesion; nominal ≥T3 (recurrent lesion ≥4 cm in diameter or minor bone erosion or deep invasion >6 mm measured from the granular layer of normal adjacent epithelium); poorly differentiated histology and ≥20 mm diameter of recurrent lesion • Completion of curative-intent post-operative RT (concurrent chemoradiotherapy is acceptable) within 2–10 weeks of randomisation • ECOG PS ≤1 • Adequate hepatic, renal, and bone marrow function • Toxicities from radiation therapy must have resolved to grade 1 or less[b]	
Main exclusion criteria (if any apply)	• SCCs arising in non-cutaneous sites • Concurrent malignancy other than localised CSCC and/or history of malignancy other than localised CSCC within 3 years of date of randomisation, except for tumours with negligible risk of metastasis or death • Patients with haematologic malignancies (note: patients with CLL are not excluded if they have not required systemic therapy for CLL within 6 months of enrolment) • Patients with history of distantly metastatic CSCC (visceral or distant nodal), unless disease-free interval is at least 3 years • Ongoing or recent (within 5 years of randomisation date) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments • Participation in a study of an investigational agent or an investigational device within 4 weeks of randomisation date or 5 half-lives • Receipt of a live vaccine within 28 days of randomisation date • Prior systemic anticancer immunotherapy for CSCC	

Trial name: C-POST	NCT number: NCT03969004
	• Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of Libtayo or placebo • Received treatment with an approved anticancer systemic therapy within 4 weeks of randomisation date or has not yet recovered from any acute toxicities except for laboratory changes described in inclusion criteria • Prior allogeneic stem cell transplantation or autologous stem cell transplantation • Patients who have permanently discontinued anticancer immune-modulating therapies due to drug-related toxicity • Encephalitis, meningitis, or uncontrolled seizures in the year prior to screening/enrolment • Myocardial infarction within 6 months prior to randomisation date • Any infection requiring hospitalisation and/or intravenous antibiotic therapy within 2 weeks of randomisation date • Active tuberculosis • Uncontrolled infection with HIV, hepatitis B virus, or hepatitis C virus; or diagnosis of immunodeficiency • History of immune-related pneumonitis within the last 5 years • History of interstitial lung disease (eg, idiopathic pulmonary fibrosis, organising pneumonia) or active, non-infectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management
Intervention	Cemiplimab/Cemiplimab-rwlc/Libtayo©/REGN2810, 350mg Q3W for 48 weeks (65/205 patients) OR 350mg Q3W for 12 weeks followed by 700mg Q6Wfor 36 weeks (140/205 patients).
Comparator(s)	Placebo Q3W for 48 weeks (64/204 patients) OR Q3W for 12 weeks followed by 700mg Q6Wfor 36 weeks (140/204 patients).
Follow-up time	Median follow-up of 24 months (range 2-64)
Is the study used in the health economic model?	No HE model.
Primary, secondary and exploratory endpoints	Median follow-up in this study was 24 months (range 2-64). Data cutoff 04. Oct. 2024. (10) Primary endpoint

Trial name: C-POST	NCT number: NCT03969004
	-Disease-free survival (DFS): time from randomization to the first documented disease recurrence by investigator assessment or death due to any cause, whichever first. Secondary endpoints -Freedom from locoregional recurrence (FFLRR) -Freedom from distant recurrence (FFDR) -Cumulative occurrence of second primary CSCC tumours (SPTs) -Overall survival (OS) -Safety, including treatment-emergent adverse events (TEAEs) -Libtayo concentrations in serum and immunogenicity as measured in antidrug antibodies in serum Radiological assessments were performed at screening and at the end of each 12-week cycle during treatment. In the follow-up period, clinical and radiological assessments were performed every 4 months for 2 years and every 6 months after. Tertiary endpoints -HRQoL as assessed by the EORTC QLQ-C30 and EQ-5D-5L [State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results must be provided in Appendix D.] Other endpoints not addressed in study: -Pattern of failure, assessed using descriptive analysis of percentages of patients in which disease recurrence for the primary endpoint of the study is due to recurrence (local, regional, or distant) -Geographic variations in administration of post-operative RT -General health status and health utility, as assessed using the EQ-5D-3L -Association between the clinical efficacy of Libtayo and molecular features of pre-treatment tumour samples -Associations between clinical efficacy of Libtayo and pre-treatment plasma circulating tumour DNA detection
Method of analysis	The primary endpoint of DFS was analysed by a stratified log-rank test at 2-sided 0.05 significance level using anatomical region of resected high-risk tumour (head and neck vs non-head and neck) and geographical region (North America vs Australia/New Zealand vs ROW) as stratification factors. Analyses were based on the full analysis set (FAS) according to treatment group and strata assigned at randomisation. Kaplan-Meier estimates including median DFS and DFS at specific time points (eg, 12, 24, 36, and 48 months), along

Trial name: C-POST	NCT number: NCT03969004
	with 2-sided 95% CIs, were presented for each treatment group. Kaplan-Meier curves were presented for each treatment group. The HR of DFS and its 95% CI were estimated by a stratified Cox regression model using the treatment group as a covariate and the same stratification factors as for the log-rank test (11). Subgroup analyses were performed to determine the consistency of treatment effect across various demographics and baseline characteristics (11).
Subgroup analyses	Subgroup analyses were performed to determine the consistency of treatment effect across various demographics and baseline characteristics. Subgroup analyses were summarised descriptively and were not formally statistically tested. Between-group treatment effect, along with its nominal 95% CI, for the primary endpoint were estimated for each of the following pre-specified subgroups (47): • Age group 1 (<65 years, ≥65 years) • Age group 2 (≥65 to <75 years, ≥75 years) • Gender (male, female) • Race (White, non-White) • Anatomic region of resected high-risk tumour (head and neck, non-head and neck) • Geographic region (North America, Australia/New Zealand, ROW) • High-risk feature (nodal, exclusively non-nodal) • ECOG PS status (0, 1) • History of CLL (presence, absence) A pre-specified exploratory analysis was conducted to compare DFS between patients treated with Libtayo and those treated with placebo within the PD-L1 biomarker subsets defined by ≥1% and <1% tumour cell expression by immunohistochemical assay
Other relevant information	

Appendix B. Efficacy results per study

Results per study

Results of the C-POST trial, DCO 04-10-2024 are presented below. The median follow-up from randomization to the data cut-off date was 24 months (range 2-64). The FAS included all randomized patients and is the intention-to-treat population based on the treatment allocated at randomization (11). All efficacy data and methods are taken from Rischin et al. 2025, the study protocol, and the study CSR (10, 11, 47).

Table 46 Results per C-POST study DCO1 Oct 2024

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median DFS	Cemiplimab	209	NR (NE, NE)	NA	NA	NA	HR: 0.32[a][b]	0.20 - 0.51	P<0.0001	DFS was analysed by a stratified log-rank test at 2-sided 0.05 significance level. Kaplan-Meier estimates including median DFS and DFS at specific time points (eg, 12, 24, 36, and 48 months), along with 2-sided 95% CIs, were presented for each treatment group. The HR of DFS and its 95% CI were estimated by a stratified Cox regression	Rischin et al, 2025.(10)
	Placebo	206	49.4 (48.5, NE)								

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										model using the treatment group as a covariate and the same stratification factors as for the log-rank test.	
Median FFLRR	Cemiplimab	209	NR (NE, NE)	NA	NA	NA	HR: 0.20[a][b	0.09 - 0.40	Not reported	All secondary endpoints were summarised descriptively and were not statistically tested. Medians estimated using KM method. HRs based on stratified proportional hazards model (cemiplimab vs. Placebo). Stratifications by high-risk tumour location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.	
	Placebo	206	NR (NE, NE)								
Median FFDR	Cemiplimab	209	NR (NE, NE)	NA	NA	NA	HR: 0.35 [a][b	0.17, 0.72	Not reported	All secondary endpoints were summarised	

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Placebo	206	NR (NE, NE)							descriptively and were not statistically tested. Medians estimated using KM method. HRs based on stratified proportional hazards model (cemiplimab vs. Placebo). Stratifications by high-risk tumour location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.	
No. Patients with at least 1 SPT	Cemiplimab	209	31 (14.8%)	NA	NA	NA				All secondary endpoints were summarised descriptively and were not statistically tested. SPTs counted as total numbers.	
	Placebo	206	37 (18%)								
Median OS	Cemiplimab	209	NR (NE, NE)	NA	NA	NA	HR: 0.863[a][b	0.391 - 1.90	Not reported	All secondary endpoints were summarised	

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Placebo	206	NR (NE, NE)							descriptively and were not statistically tested. Medians estimated using KM method. HRs based on stratified proportional hazards model (cemiplimab vs. Placebo). Stratifications by high-risk tumour location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.	
Estimated event-free probability, DFS, %: 3 months	Cemiplimab	209	95.9 (92.0, 97.9)	NA						Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs will be presented for each treatment group. Kaplan-Meier curves will be	
	Placebo	206	90.2 (85.0, 93.6)	NA							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
6 months	Cemiplimab	209	94.3 (89.9, 96.8)	NA						presented for each treatment group	
	Placebo	206	79.9 (73.5, 85.0)	NA							
12 months	Cemiplimab	209	92.4 (87.5, 95.5)	NA							
	Placebo	206	69.5 (62.1, 75.7)	NA							
24 months	Cemiplimab	209	87.1 (80.3, 91.6)	NA							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	206	64.1 (55.9, 71.1)	NA							
36 months	Cemiplimab	209	83.1 (74.9, 88.9)	NA							
	Placebo	206	60.4 (51.1, 68.5)	NA							
48 months	Cemiplimab	209	80.5 (70.5, 87.4)	NA							
	Placebo	206	60.4 (51.1, 68.5)	NA							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Estimated event-free probability, FFLRR, %: 3 months	Cemiplimab	209	98.4 (95.3, 99.5)	NA						Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs will be presented for each treatment group. Kaplan-Meier curves will be presented for each treatment group	
	Placebo	206	92.2 (87.4, 95.2)	NA							
6 months	Cemiplimab	209	98.4 (95.3, 99.5)	NA							
	Placebo	206	85.5 (79.6, 89.8)	NA							
12 months	Cemiplimab	209	96.6 (92.5, 98.5)	NA							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	206	79.1 (72.2, 84.4)	NA							
24 months	Cemiplimab	209	94.6 (89.1, 97.3)	NA							
	Placebo	206	76.7 (69.1, 82.6)	NA							
36 months	Cemiplimab	209	92.9 (85.8, 96.5)	NA							
	Placebo	206	74.1 (64.7, 81.3)	NA							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Estimated event-free probability, FFDR, %: 3 months	Cemiplimab	209	98.0 (94.7, 99.2)	NA						Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs were used for each treatment group.	
	Placebo	206	96.9 (93.2, 98.6)	NA							
6 months	Cemiplimab	209	96.3 (92.3, 98.2)	NA							
	Placebo	206	92.8 (87.9, 95.8)	NA							
12 months	Cemiplimab	209	96.3 (92.3, 98.2)	NA							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	206	86.2 (79.6, 90.7)	NA							
24 months	Cemiplimab	209	94.3 (89.0, 97.1)	NA							
	Placebo	206	83.8 (76.3, 89.0)	NA							
36 months	Cemiplimab	209	94.3 (89.0, 97.1)	NA							
	Placebo	206	81.9 (73.6, 87.9)	NA							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Estimated survival probability, %: 6 months	Cemiplimab	209	98.5 (95.3, 99.5)	NA						Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs will be presented for each treatment group. Kaplan-Meier curves will be presented for each treatment group	
	Placebo	206	99.5 (96.4, 99.9)	NA							
12 months	Cemiplimab	209	97.9 (94.4, 99.2)	NA							
	Placebo	206	98.3 (94.8, 99.5)	NA							
24 months	Cemiplimab	209	94.8 (89.6, 97.4)	NA							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	206	92.3 (86.5, 95.7)	NA							
36 months	Cemiplimab	209	89.9 (82.1, 94.4)	NA							
	Placebo	206	92.3 (86.5, 95.7)	NA							

[a] Stratified by high-risk tumour location (HN versus non-HN) and geographical region (North America versus Australia/New Zealand versus ROW) per EDC. [b] Based on stratified proportional hazards model (cemiplimab versus placebo. Abbreviations: CI, Confidence interval; DFS, disease-free survival; DR, distant recurrence; EDC, Electronic data capture (database); FFDR, freedom from distant recurrence; FFLRR, freedom from locoregional recurrence; HN, Head and neck; HR, Hazard ratio; KM, Kaplan-Meier; LR, locoregional recurrence; NA, Not applicable; NE, Not established; NR, Not reached; OS, overall survival; ROW, Rest of world; SPT, second primary tumour.

Results of the unpublished C-POST trial DCO2 (07 April 2025) are presented below.

Table 47 Results per C-POST study, DCO2 07 April 2025

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DFS was analysed by a stratified log-rank test at 2-sided 0.05 significance level. Kaplan-Meier estimates including median DFS and DFS at specific time points (eg, 12, 24, 36, and 48 months), along with 2-sided 95% CIs, were presented for each treatment group. The HR of DFS and its 95% CI were estimated by a stratified Cox regression model using the treatment group as a covariate and the same stratification factors as for the log-rank test.	Regeneron data on file (53)
[redacted]	[redacted]	[redacted]	[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All secondary endpoints were summarised descriptively and were not statistically tested. Medians estimated using KM method. HRs based on stratified proportional hazards model (cemiplimab vs. Placebo). Stratifications by high-risk tumour location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.	
	[redacted]	[redacted]	[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	[redacted]	[redacted]	[redacted]							All secondary endpoints were summarised descriptively and were not statistically tested. Medians estimated using KM method. HRs based on stratified proportional hazards model (cemiplimab vs. Placebo). Stratifications by high-risk tumour location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]			All secondary endpoints were summarised descriptively and were not statistically tested. SPTs counted as total numbers.	
	[redacted]	[redacted]	[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	All secondary endpoints were summarised descriptively and were not statistically tested. Medians estimated using KM method. HRs based on stratified proportional hazards model (cemiplimab vs. Placebo). Stratifications by high-risk tumour location (HN vs non-HN) and geographical region (North America vs Australia/New Zealand vs ROW) per EDC.	
	[redacted]	[redacted]	[redacted]								

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs will be presented for each treatment group. Kaplan-Meier curves will be presented for each treatment group	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
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	[redacted]	[redacted]	[redacted]	[redacted]							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs will be presented for each treatment group. Kaplan-Meier curves will be presented for each treatment group	
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs were used for each treatment group.	
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]							

Results of C-POST trial (NCT03969004)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						Kaplan-Meier estimates including median and event-free rate at the end of each year, along with 2-sided 95% CIs will be presented for each treatment group. Kaplan-Meier curves will be presented for each treatment group	
	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							

[a] Stratified by high-risk tumour location (HN versus non-HN) and geographical region (North America versus Australia/New Zealand versus ROW) per EDC. [b] Based on stratified proportional hazards model (cemiplimab versus placebo. Abbreviations: CI, Confidence interval; DFS, disease-free survival; DR, distant recurrence; EDC, Electronic data capture (database); FFDR, freedom from distant recurrence; FFLRR, freedom from locoregional recurrence; HN, Head and neck; HR, Hazard ratio; KM, Kaplan-Meier; LR, locoregional recurrence; NA, Not applicable; NE, Not established; NR, Not reached; OS, overall survival; ROW, Rest of world; SPT, second primary tumour.

Appendix C. Comparative analysis of efficacy

N/A

Appendix D. Extrapolation

N/A

Appendix E. Serious adverse events

The tables below present the total number of patients with at least one treatment-emergent SAE, with further specification of AE by system organ class and preferred term for those experienced by more than 1% of the treated population in either arm.

Table 48 Serious adverse events DCO1, 04 Oct 2024 (10, 11)

Preferred term	Cemiplimab (N=205), n (%)	Placebo (N=204), n (%)
Number of patients with at least one treatment emergent serious adverse event	36 (17.6%)	19 (9.3%)
Infections and infestations	10 (4.9%)	9 (4.4%)
Pneumonia	2 (1.0%)	2 (1.0%)
Cellulitis	1 (0.5%)	2 (1.0%)
Skin infection	0	2 (1.0%)
Endocrine disorders	3 (1.5%)	0
Adrenal insufficiency	2 (1.0%)	0
Gastrointestinal disorders	3 (1.5%)	1 (0.5%
Diarrhoea	2 (1.0%)	0

Note – total patients for cemiplimab (N=205) and placebo (N=204) exclude the 4 cemiplimab-arm patients and the 2 placebo-arm patients who did not receive treatment. Refer to patient disposition Figure 3.

Table 49 Serious adverse events DCO2, 07 Apr 2025 (53)

Preferred term	Cemiplimab (N=205), n (%)	Placebo (N=204), n (%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

N/A

Appendix H. Literature searches for the clinical assessment

N/A

Appendix I. Literature searches for health-related quality of life

N/A

Appendix J. Literature searches for input to the health economic model

N/A

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