NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592) [ID3883]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592) [ID3883]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from **Sanofi**
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submission** from:
   a. British Association of Dermatologists (BAD)
4. **SACT report**
5. **Evidence Review Group report** prepared by Southampton Health Technology Assessments Centre
6. **Evidence Review Group – factual accuracy check**
7. **Technical engagement response** from **Sanofi**
8. **Technical engagement response & expert statement from experts:**
   a. Andrew Sykes – clinical expert, nominated by Sanofi
9. **Technical engagement response from consultees and commentators:**
   a. British Association of Dermatologists
10. **Evidence Review Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessments Centre

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA592

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma [ID:3883]

Company evidence submission for committee

January 2022

File name	Version	Contains confidential information	Date
ID3883_Cemiplimab in aCSCC v.Final (v5.0) AIC CIC MARKED 20220511	**V5.0**	**Yes**	**11th May 2022**

Instructions for companies

This is the template you should use for your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the Cancer Drugs Fund (CDF) review process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision making.

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If applicable provide any supportive and detailed methodological or investigative evidence (additional to the clinical trial and/or Systemic Anti-Cancer Therapy data) in an appendix to this submission.

When cross referring to evidence in the original submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/Figure name – document, heading, subheading (page X).Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Cancer Drugs Fund review submission

A.1 Background

- The outcome of the NICE TA592 appraisal process recommended cemiplimab as monotherapy for use in the Cancer Drugs Fund (CDF) to treat adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. The cemiplimab licence states cemiplimab should be continued until disease progression or if there is unacceptable toxicity (whichever occurs first), however the NICE recommendation includes a stopping rule following 2 years of treatment analogous to the EMPOWER-CSCC 1.
- The committee acknowledged the unmet need within the target population and accepted that cemiplimab had the potential to be cost-effective, but more evidence was needed to address clinical uncertainties.
- The key sources of uncertainty highlighted by the committee during TA592 include:
  - The baseline characteristics of patients included in the model and their generalisability to UK clinical practice.
  - Long-term treatment benefit of cemiplimab. In particular, the magnitude of any continued treatment benefit after a stopping rule
  - Lack of reliable comparative evidence that is generalizable to UK clinical practice
- The committee noted that clinical data from the ongoing Phase II cemiplimab clinical trial, EMPOWER-CSCC 1 (Study 1540), will be the primary source of data to address uncertainties associated with cemiplimab. The committee also noted an on-going retrospective chart review study and suggested data from this study should be incorporated in the indirect treatment comparisons and the economic evaluation.

A.2 Key committee assumptions

Key committee assumptions as per the terms of engagement are presented in Table 1, with comments from Sanofi added below key assumptions.

Table 1: Key committee assumptions as per the terms of engagement

Area	Committee preferred assumptions
Population	The final scope stated the population as people with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) in whom there is no curative local therapy. This aligned with the marketing authorisation which specified those who are not candidates for curative surgery or curative radiation. During technical engagement it was agreed that people with significant autoimmune disease or who have had a solid organ transplant are unlikely to be eligible for treatment. **Adults with metastatic or locally advanced cutaneous cell carcinoma that is not appropriate for curative surgery or curative radiotherapy are the relevant population for the CDF review.** **Sanofi** agree and would like to emphasize the high unmet need and disease burden associated with these patients. The clinical community has also suggested that people with autoimmune disease or who have had a solid organ transplant may benefit from cemiplimab and believe it would extend the life of these patients.
Comparators	Cemiplimab is an appropriate treatment option for people who would otherwise be offered chemotherapy. It is also appropriate for some people who would be offered best supportive care. The committee agreed that chemotherapy and best supportive care are both relevant comparators. **The company should present clinical and cost-effective evidence for cemiplimab compared to chemotherapy and best supportive care (BSC).** **Sanofi** consider both platinum-based chemotherapy and BSC relevant comparators. There is an absence of established treatment options for these patients, which was a key rationale for EMPOWER-CSCC-1 being a single arm trial. Following further consultation with UK clinicians since the availability of cemiplimab on the CDF, it has been noted that in clinical

Area	Committee preferred assumptions
	practice BSC may now be considered a more relevant comparator as cemiplimab can be used in patients who may not be able to tolerate chemotherapy. It is however difficult to capture BSC patients in studies, as they are often managed in primary care and much of the evidence required for a full economic evaluation is based on patients receiving platinum-based chemotherapy.
Generalizability of trial evidence	The evidence came from two single arm trials, one Phase I and one Phase II trial (EMPOWER-CSCC 1). The base case analysis included two of the three groups in the Phase II trial which were combined with the Phase I trial in an integrated analysis (combined n = 193). A key issue was the dosing regimens. All 193 people had a weight-based dose of 3 mg /kg every 2 weeks. The licensed dose is 350 mg every 3 weeks and data on this was limited to 44 patients in the third group of the Phase II trial, which was not included in the integrated analysis. This group also had a shorter follow-up than the other two groups. The company did a scenario analysis using this data on the licensed dose, but the committee decided it was inconclusive due to the small number of patients. The committee accepted that the generalisability of the dosing was an area of uncertainty. The committee also noted that the average age of people in the trial was lower than would be expected in clinical practice for people with advanced disease. However, the clinical experts explained that those who were most likely to benefit from treatment would likely be younger than the average age of people with advanced unresectable CSCC. The committee concluded that trial data are likely to be generalisable to the NHS but recognised that there are some key uncertainties. **The company should use data collected through the Systemic Anti-Cancer Therapy (SACT) Dataset to demonstrate the generalizability of the trial data.** **Sanofi** noted numerical errors above, the correct number of patients in the combined Phase I and Phase II trials is 219 as of the October 2017 Data cut off (DCO) and consistently in the July 2021 DCO. (Phase I, n= 26; Phase II n=193). In the initial Company submission TA592, the number of patients in the integrated analysis was 108, since TA592, a further 33 patients

Area	Committee preferred assumptions
	have been enrolled into EMPOWER CSCC that have received the flat dose of 350 mg every 3 weeks. At the time of the data cut (July 2021) analysed within this submission, the number of patients with the group receiving 350mg every three weeks is 56. The use of SACT data within this submission is detailed in section A.6
Survival outcomes	The committee noted that the overall response rates and median PFS reported in the trials were encouraging. In addition, the committee felt that the fact that the median overall survival (OS) had not yet been reached suggested a promising treatment benefit. However, the committee recalled the uncertainties regarding generalizability of the data, and that both trials were single arm with no comparative data. In addition, the trial data were immature with 70% of patients still alive in the Phase II trial. The duration of treatment effect and OS for people having cemiplimab was unknown. Overall, the committee concluded that the survival outcome data was promising but uncertain. **The company should use updated survival data from EMPOWER-CSCC 1 and fully explore the most appropriate method to extrapolate survival outcomes. Data collected through SACT should be used to validate the trial outcomes.** **Sanofi** have provided results within this submission using updated survival data from EMPOWER-CSCC 1
Comparator data	The comparator data are limited. The clinical effectiveness estimates used in the company's base case came from a subset of 18 patients who had platinum-based chemotherapy in a non-UK retrospective chart review (Jarkowski et al). Another retrospective study was published after the company made its original submission which included a subset of 36 patients with unresectable skin lesions on the head and neck (Sun et al. 2019). Clinical experts were concerned that the Jarkowski data suggested more prolonged survival than is typically seen in clinical practice and thought the Sun et al. study was more reliable. The committee noted that both studies had

Area	Committee preferred assumptions
	limitations due to the populations, study designs and sample sizes. The committee concluded that none of the data provided a reliable estimate of clinical outcomes for chemotherapy or best supportive care. The committee understood that the company was conducting a retrospective chart review of patients who have had existing treatments in the UK and whilst recognising limitations with the study design, felt that the larger sample size and inclusion of 106 UK patients would be a better source of comparator data in the absence of any controlled trial data. The clinical experts highlighted that the OS estimates used in the model do not align with their clinical experience. The committee was concerned but could not comment on the reliability of the modelled projections for OS due to limitations in the data underpinning the extrapolations **The company should use their UK chart review and any additional data that has become available during the period of managed access to inform the comparator arms.** **Sanofi** agrees the UK chart review data is the most reliable source of comparator data available. Sanofi have continued to engage with the clinical community, who are still of the opinion that much of the literature overestimates survival compared to clinical practice, as these participants are often selected based on their ability to be treated. Clinicians suggested that in clinical practice more patients would receive BSC than chemotherapy. To clarify, the retrospective study, Sun et al. 2019 contains BSC patients whereas the chart review and Jarkowski 2016 are used to inform comparisons with chemotherapy.
Relative effectiveness	As the trials were single arm, an indirect treatment comparison (ITC) was needed to establish the relative effectiveness of cemiplimab. The company explored three methods: a naïve comparison, a simulated treatment comparison and matching-adjusted indirect comparison (MAIC). The company used the naïve comparison to inform its base case. The committee concluded that the relative effectiveness estimates for cemiplimab are highly uncertain regardless of ITC method as all used unreliable comparator data.

Area	Committee preferred assumptions
	The company should fully explore the most appropriate treatment comparison method and utilize any updated data that has become available during the period of managed access. **Sanofi** have explored different statistical methods within this submission to compare the datasets, see section A.6.6.
Treatment effect duration	The company included a 24-month stopping rule in its base case and assumed that the benefit of cemiplimab would last for 3 years in total (at this point the hazards for cemiplimab become equal to those used in the chemotherapy arm). The committee considered that these assumptions are reasonable but are not evidence based and are therefore uncertain. The committee also had concerns about the generalizability of the trial evidence given the variation in treatment duration. Twenty-six patients in the base case analysis had treatment for up to 11 months but the remaining 123 had treatment for 22 months. The marketing authorisation did not include a stopping rule but a 24-month stopping rule is included in the recommendation. **The company should use updated survival data from EMPOWER-CSCC 1 and fully explore the impact of a 24-month stopping rule on long-term outcomes.** **Sanofi** align to this assumption within TA592, exploring the stopping rule using the updated EMPOWER CSCC-1 data.
Most plausible ICER	The company's base case incremental cost-effectiveness ratio (ICER) was £45,693 per quality-adjusted life year (QALY) gained compared with chemotherapy and £47,463 per QALY gained compared with best supportive care. The ICERs in all the scenario analyses are higher than the £30,000 per QALY gained. Due to uncertainty in the evidence base, the committee did not state a preferred ICER but accepted that many of the assumptions in the company's base case appeared reasonable.

Area	Committee preferred assumptions
	The committee felt there was a possibility that end-of-life criteria could be met and if this were the case then the ICERs would be cost-effective. **The committee agreed that cemiplimab demonstrated plausible potential to be cost-effective.** **Sanofi** note that the results within this submission demonstrate that cemiplimab is cost effective using the updated data. See section A.8
End-of-life	The committee accepted that the data presented did not support application of the end-of-life criteria at present primarily due to the extrapolated life expectancy in the comparator arm being greater than 24 months. However, due to the uncertainty in the survival data and modelled OS projections, and the fact that these do not align with the experience of the clinical experts, the committee felt there was a possibility that cemiplimab could meet the end-of-life criteria. **The company should demonstrate whether cemiplimab meets the end-of-life criteria** **Sanofi** note that the available data demonstrate that cemiplimab meets end-of-life criteria. This is detailed in section A.13

A.3 Other agreed changes

The only additional changes outside of what was recommended in the Managed Access Agreement (MAA), are those related to the minor updates in the cost-effectiveness model, identified since the initial appraisal and are as outlined in Appendix A.15.12.

The economic model includes a toggle within the “Model parameter” worksheet cell C80, that restores inputs back to the ERG base case 2018. A detailed change log (worksheet named “Change log”) is also included within the model.

A.4 The technology

A summary of cemiplimab is provided in Table 2.

Table 2: A summary of the technology

UK approved name and brand name	Cemiplimab (Libtayo®)
Mechanism of action	Cemiplimab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor, an immune checkpoint involved in T-cell differentiation and function. PD-1 binds to its ligands PD-L1 and PD-L2 on cell surfaces and imparts an inhibitory signal to T-cells. Tumours hijack this pathway by expressing PD-L1 thus allowing tumour cells to evade normal recognition by the immune system. By evading the immune system, tumour cells effectively form a microenvironment suitable for proliferation. By binding to PD-1, cemiplimab blocks the engagement of PD-1 to PD-L1, resulting in reactivation of T-cell receptor signalling and thus restoring human immune surveillance to elicit an anti-tumour response.[1]
Marketing authorisation/CE mark status	An application was filed in March 2018 to the European Medicines Agency (EMA) to allow cemiplimab to be used to treat advanced CSCC. Committee for Medicinal Products for Human Use opinion and a conditional marketing authorisation were received July 2019 Conversion to full marketing authorisation is anticipated in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics	<u>Cutaneous Squamous Cell Carcinoma</u> Cemiplimab 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 <u>Basal Cell Carcinoma</u> Cemiplimab 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). <u>Non-Small-Cell Lung Cancer</u> Cemiplimab 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 epidermal growth factor receptor (EGFR), ALK or ROS1 aberrations, who have: – locally advanced NSCLC who are not candidates for definitive chemoradiation, or – metastatic NSCLC
Method of administration and dosage	Administration is via intravenous (IV) infusion over 30 minutes through an IV line containing a sterile, in line or add-on filter (0.2 micron to 5 micron pore size).

	The licensed dose of cemiplimab is 350 mg every 3 weeks. Treatment may be continued until disease progression or unacceptable toxicity.
Additional tests or investigations	No additional tests or investigations are required
List price and average cost of a course of treatment	The list price for cemiplimab is £4,650 per 350 mg vial. With a dosing regimen of 350 mg every 3 weeks. £4,650 is also the cost of cemiplimab per treatment cycle. Patients will be treated with cemiplimab until progression or unacceptable toxicity. The cost for a year of treatment with cemiplimab based on the list price is £80,877.
Commercial arrangement (if applicable)	The company have provided a simple patient access scheme for cemiplimab of [redacted]The discounted price per 350 mg vial is[redacted]
Date technology was recommended for use in the CDF	July, 2019
Data collection end date	July, 2021

A.5 Clinical effectiveness evidence

Table 3: Clinical evidence for cemiplimab

Study title	**Phase 1 Study (Study 1423) (NCT02383212)**	**Phase II EMPOWER-CSCC 1 (Study 1540) (NCT02760498)**	**Cemiplimab SACT data cohort study [new data]**
Study design	Phase I, first in human, open-label, dose escalation, cohort expansion, non-comparative, multicentre study	Phase II, non-randomized, non-comparative, three-group, multicentre study	SACT data cohort study
Population	Adults with advanced solid tumours, including cohorts of patients with mCSCC or laCSCC who were not candidates for surgery with ECOG PS 0-1	Adults with mCSCC or laCSCC who were not candidates for surgery or radiotherapy with ECOG PS 0-1	Patients with locally advanced or metastatic cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation
Intervention(s)	Cemiplimab 3 mg /kg IV Q2w up to 48 weeks	Cemiplimab 3 mg /kg IV Q2w until progression or up to 96 weeks (22 months) Cemiplimab 350 mg fixed dose IV Q3w until progression or up to 54 weeks	Cemiplimab 350mg fixed dose IV Q3w until disease progression or up to 2 years.
Comparator(s)	Not applicable	Not applicable	Not applicable
Outcomes collected that address committee's key uncertainties	• ORR • DoR • **PFS *(new data July 2021)*** • **OS *(new data July 2021)*** • **Safety**	• **OS *(new data July 2021)*** • **PFS (IRC assessed) *(new data July 2021)*** • Treatment duration • **Safety (*new data July 2021*)** • **HRQoL (n*ew data October 2020*)**	Patient/disease characteristics • OS • TTD

Reference to section in appendix	Sections A.6.1.3 and A.8.4.1 and Appendix A.15.3	Sections A.6.1.2 and A.8.3.1 and Appendix A.15.2	Section A.7.3 (page 40)
Key: DOR, Duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health related quality of life; IRC, independent review committee; laCSCC, locally advanced cutaneous cell carcinoma; mCSCC, metastatic cutaneous cell carcinoma; ORR, Overall response rate; OS, overall survival; PFS, progression-free survival; Q2w, every 2 weeks; Q3w, every 3 weeks. TTD, time to treatment discontinuation. **BOLD text** represents outcomes that the model incorporated.			

Table 4: Clinical evidence for comparators

Study title	UK Retrospective Chart review study (new data)	Sun 2019 (new publication identified during TA592)	Jarkowski 2016 (used in NICE TA592)
Study design	• Retrospective, observational, multi-centre, cohort study with data abstracted from the medical records of patients with advanced CSCC	• Retrospective, observational, chart review study	• Retrospective, observational, review of patient medical records with CSCC
Population	• Data were collected for patients treated with chemotherapy with: – locally advanced cutaneous squamous cell carcinoma (laCSCC) - defined as those with inoperable tumours and those ineligible for radiation therapy for the target lesion who are not candidates for surgery – metastatic cutaneous squamous cell carcinoma (mCSCC) - defined as those with local/regional nodal as well as distant metastasis • Patients were excluded if they were diagnosed with carcinoma that originated in the mucous membranes of the head and neck, anus, genitals, lung, and/or if they were immune suppressed/immunocompromised.	• Patients with mCSCC	• Patients with unresectable laCSCC or mCSCC treated with systemic therapy from January 2001 to January 2011 were reviewed

Intervention(s)	• No treatment • Platinum base chemotherapy • Platinum base chemotherapy + fluorouracil (5FU) • Other chemotherapy • Chemotherapy + EGFR-I • EGFR-I • Interferon alfa	• Best supportive care Management included: - Salvage surgery (n=9) - including 4 patients with postoperative re-irradiation - Palliative RT (n=21) - Palliative chemotherapy (n=4) - Cetuximab (n=2) - Hospice care with no further therapy (n=9) - No data on salvage management (n=27)	• Systemic anticancer therapy – Capecitabine – Cetuximab – Platinum – Taxane
Comparator(s)	Not applicable	Not applicable	Not applicable
Outcomes collected that address committee's key uncertainties	**OS** PFS*	**OS**	**OS** **PFS**
Reference to section in appendix	Section A.6.2 and Appendix A.15.5	Section A.6.4 and Appendix A.15.9	Section A.6.3 and Appendix A.15.9

* defined as date of visit when the progression is documented

Key: EGFR-I, Epidermal growth factor receptor-inhibitors; laCSCC, locally advanced cutaneous cell carcinoma; mCSCC, metastatic cutaneous cell carcinoma; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; TTD, time to treatment discontinuation.

A.6 Key results of the data collection

Extended follow-up data reported from the EMPOWER-CSCC 1 study (July 2021) includes a maximum of [redacted] months' follow-up. Overall survival (OS) and progression-free survival (PFS) data were collected to address key uncertainties raised during the TA592 appraisal.[2] The updated survival data from EMPOWER-CSCC 1 is consistent with the survival data and extrapolations presented in TA592 and provides additional long-term evidence to support the use of cemiplimab and the continuing treatment benefit associated with cemiplimab in metastatic and locally advanced CSCC. For consistency, health state utility and safety data from the updated data cuts were incorporated in the economic model and are reported in the Appendix A.15.10 and A.15.11 respectively.

The comparators considered in the model are platinum-based chemotherapy and best supportive care (BSC) [where treatment options are palliative in nature]. To address uncertainties in the generalisability of comparative evidence to the UK, survival data were collected via a retrospective chart review and these data are included in the economic model. The retrospective chart review only identified [redacted] patients treated with BSC, of these only [redacted] patients had a performance status of ≤1 and would be deemed similar to patients entered into EMPOWER-CSCC 1. Clinical experts suggest that the small number of BSC patients identified as part of the chart review is likely due to this group of patients being discharged to receive palliative care within the primary care setting.

The updated systematic literature review did not identify any additional relevant comparator publications other than the retrospective study by Sun et al. 2019.[3] This publication was identified by the ERG during TA592; at the time clinical experts considered this a more reliable source for BSC data and is included to inform comparative evidence for BSC.

SACT data collected over the two-year period within the CDF were considered as a potential supplementary data source.

A.6.1 EMPOWER-CSCC 1 study

A.6.1.1 Dosing regimen

This submission includes data from three groups (Table 5), including data from the full cohort of group 3, which was not available during the TA592 appraisal process. Results between groups, remain consistent, supporting the 350 mg every three weeks flat dosing which forms the conditional marketing authorisation from the EMA.

Table 5: Dosing regimens groups within EMPOWER CSCC-1

Group	n	Regimen
Group 1	59	patients with mCSCC, receiving 3 mg/kg intravenous (IV) cemiplimab every 2 weeks for up to 96 weeks
Group 2	78	patients with laCSCC who were not candidates for surgery or radiation, receiving 3 mg/kg IV cemiplimab every 2 weeks for up to 96 weeks
Group 3	56	patients with mCSCC, receiving a flat dose cemiplimab, 350 mg IV every 3 weeks for up to 54 weeks

CSCC: Cutaneous skin cell carcinoma; IV, Intravenous, kg, kilograms; laCSCC, Locally advanced CSCC; mCSCC, metastatic CSCC; mg, milligrams

A.6.1.2 Overall survival

One of the considerations noted in the MAA was the long-term survival benefit associated with cemiplimab, in particular the magnitude of any continued benefit after treatment cessation. Figure 1 presents OS Kaplan–Meier (KM) plots from the latest EMPOWER-CSCC 1 data cut-off (DCO) (July 2021, maximum [redacted] months follow-up, median follow-up [redacted] months), alongside the October 2017 data cut used to inform TA592. Patients within EMPOWER-CSCC 1 adhered to a stopping rule of 22 months, progression, or death, whichever was sooner. In the latest data cut, cemiplimab continues to demonstrate strong survival outcomes and shows that treatment benefit is maintained post treatment cessation. At the time of the updated July 2021 data cut, with a median follow-up of [redacted], survival was [redacted]%, and median survival has still not been reached.

Table 6. Summary statistics of results from study 1423 (Phase 1 2019 DCO) and EMPOWER CSCC-1 (Phase 2 July 2021 DCO)

	Study 1423	EMPOWER-CSCC 1
Objective response, n (%)	[redacted]	[redacted]
Complete response, n (%)	[redacted]	[redacted]

Partial response, n (%)	[redacted]	[redacted]
Stable disease, n (%)	[redacted]	[redacted]
Non-CR/Non-PD, n (%)	[redacted]	[redacted]
Progressed, n (%)	[redacted]	[redacted]
Not evaluable, n (%)	[redacted]	[redacted]
Time to response, median (95% CI) months	[redacted]	[redacted]
Observed duration of response, min:max	[redacted]	[redacted]

CI, Confidence interval; CR, Complete response; n, number; NE, Not estimated; PD, Progressive Disease

Table 7. Summary statistics for survival data from study 1423 (Phase 1 2019 DCO) and EMPOWER CSCC-1 (Phase 2 July 2021 DCO)

	Study 1423		EMPOWER-CSCC 1		
	PFS	OS	ToT	PFS	OS
Study follow-up, median (95% CI)	[redacted]		[redacted]		
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censors, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outcome follow-up, min:max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI, Confidence interval; max, Maximum; min, Minimum; n, number; NE, Not estimated; NR, Not reported; OS, Overall survival; PFS, Progression-free survival; ToT, Time on treatment

Figure 1. Kaplan–Meier plot for OS – Pooled Phase 1 and 2 Cemiplimab trials 2017 data cut presented in TA592 and 2021 data cut

DCO, Data cut off; KM, Kaplan–Meier; OS, overall survival.

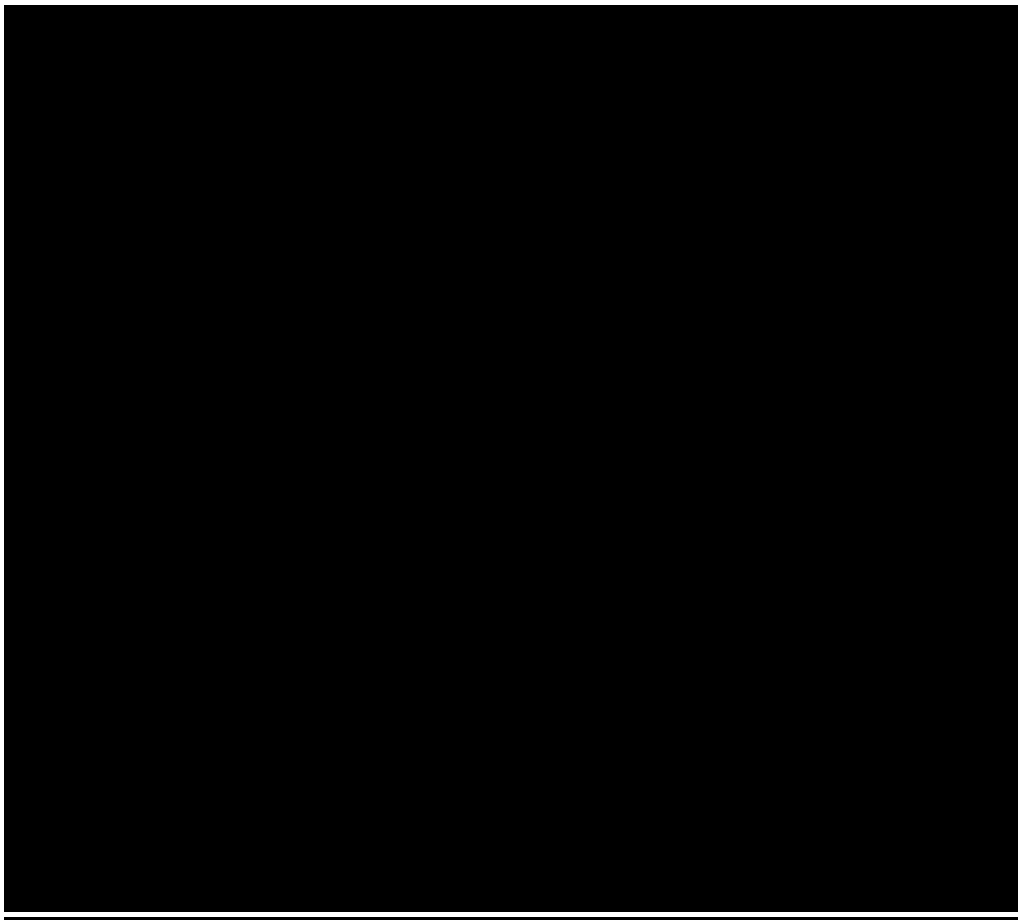
A.6.1.3 Progression-free survival

The independent review committee (IRC) was convened in September 2021 to review cases for PFS data from the EMPOWER-CSCC 1 July 2021 DCO. Figure 2 presents PFS KM plots from the July 2021 and October 2017 DCOs.

Median PFS was [redacted] in the July 2021 DCO. Cemiplimab continues to show strong PFS outcomes for the population of interest up to [redacted] months, after which there is a drop in the PFS KM estimates. However, KM data after [redacted] months are heavily censored, with only [redacted] and [redacted] patients remaining at risk at [redacted] and [redacted] months, respectively, an artifact of the follow-up duration. Therefore, data past [redacted] months becomes more susceptible to random variation, when only a small number of patients remain in the sample. The drop in the KM estimates at [redacted] months can be attributed to this random variation.

Clinical experts consulted as part of an advisory board agree that the heavily censored data at the curve tail skews the cemiplimab trial data, which otherwise they would expect to plateau.[4, 5]

Figure 2: KM curve for PFS – Pooled Phase 1 and 2 Cemiplimab trials 2017 data cut presented in TA592 and 2021 data cut



DCO, Data cut off; KM, Kaplan–Meier; PFS, Progression free survival.

A.6.2 Retrospective chart review

The retrospective chart review was conducted with the aim of collecting data to inform the treatment patterns and survival outcomes of patients with advanced CSCC in the UK that would have been eligible to participate in EMPOWER-CSCC 1.

A.6.2.1 Patient population

Efficacy for platinum-based chemotherapy in TA592 was informed by indirect treatment comparison using Jarkowski et al. 2016, a non-UK population study.[6]

During the review process the committee highlighted the lack of comparative evidence of cemiplimab versus treatments observed in current UK clinical practice for advanced CSCC. To address this, a retrospective, observational, chart review study was conducted to collect data on patients with metastatic or locally advanced CSCC between January 1, 2011, and December 31, 2015. Eligibility criteria, exclusion criteria and data collected for the chart review are presented in Appendix A.15.1.

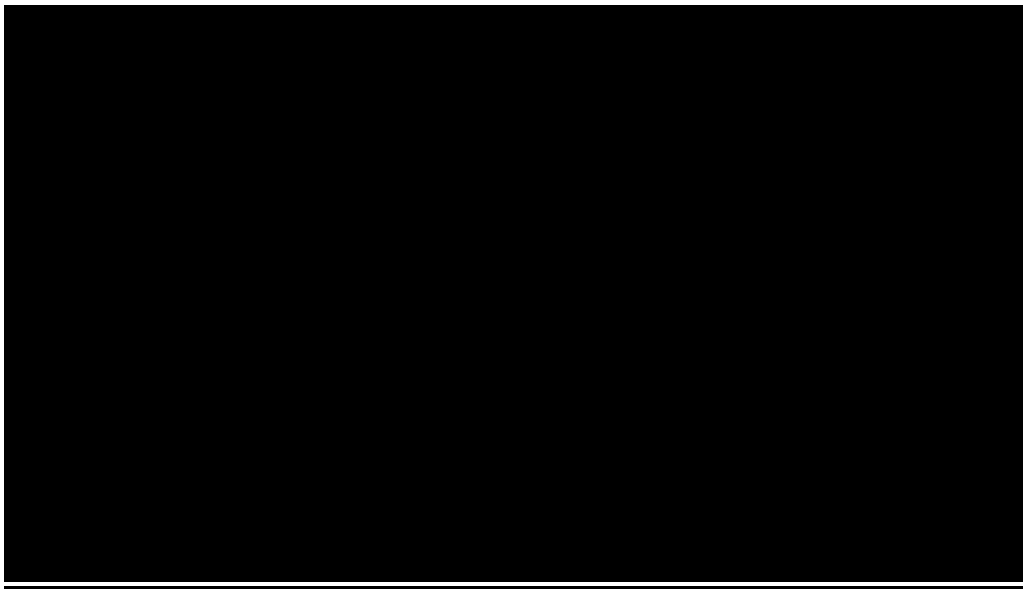
The chart review was a double-blind data collection at site and sponsor level, third-party site investigators were responsible for data abstraction and completion of CRF. Clinical expert review of the initial chart review cohort (n = 106) findings raised concerns over the robustness of the data and comparability of the chart review patient population to those in EMPOWER-CSCC 1. One of the key issues raised was related to confidence in the characterisation of surgical history/candidacy of these patients, particularly, in retrospectively identifying patients who are no longer candidates for curative surgery or radiotherapy. Based on these concerns, clinical experts recommended an audit of the chart review cohort to investigate data quality and ensure comparability.

The audit reviewed patient records for details on prior treatments and disease history, multidisciplinary decision making in the advanced setting and concomitant and subsequent treatment. The audit took place in Q4 2020, however due to the enforced restrictions on personnel allowed to access hospital grounds attributable to the COVID-19 pandemic and hospital resource constraints the audit saw limited participation (n=[redacted] patients). To maximize the use of available data, the audited data (n = [redacted]) was integrated into the original dataset (n = 106), to create enriched profiles for patients whose records were audited. The final integrated cohort dataset for analysis included [redacted] patients who were part of the audit (see Figure 3). Further detail on the audit is presented in Appendix A.15.6.

The chart review aimed to collect data that was comparable to the population recruited to EMPOWER-CSCC 1. However, on review of the data some residual differences between the retrospective chart review and EMPOWER-CSCC 1 trial populations were observed. For example, the audit identified several patients receiving biopsy considered to be partial excisions per clinical expert opinion.

Although the reason for excision biopsies was not collected, a clinical expert suggested that the biopsies were a form of tumor debulking which would render these patients incomparable to EMPOWER-CSCC 1 (i.e., locally advanced, not eligible for surgery or RT). Further, the administration of excision biopsies was concentrated across three centers suggesting variation in practice in the UK. To address these differences, several decision rules based on an analysis of the data and clinical expert opinion, were applied to the integrated chart review cohort to identify the group of advanced CSCC patients who met the inclusion criteria of EMPOWER-CSCC 1 but received treatment in real world clinical practice outside of the trial. Figure 3 presents the patient flow and decision rules for the integrated chart review population (further detail can be found in Appendix A.15.7).

Figure 3: Patient flow and decision rules for the chart review population



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; UK, United Kingdom.
Notes: ECOG PS measured from time of treatment initiation. Integrated audit population is the original chart review data combined with the audit. The decision rule excluding patients who did not receive platinum-based chemotherapy was based on first-line only, consistent with the outcome definition.

Of the 106 patients included in the cohort, [redacted] patients received at least one line of therapy, the remaining [redacted] patients aligned with the definition of patients eligible for BSC and of these only [redacted] patients had ECOG PS ≤1. An analysis of a BSC population was therefore not possible and the analysis was restricted to patients receiving platinum-based chemotherapy. The limited data availability for patients receiving

BSC in secondary care case notes is probably unsurprising given that these patients would have had no treatment options available to them. Expert clinical advice received as part of the advisory board to inform this submission, suggests that if there are no treatment options available for clinical/medical oncologists to treat these patients, they are discharged from care and these patients would instead receive palliative care within the primary care setting. This would suggest the relative absence of BSC patients in the chart review is an artifact of the data source. A UK clinician consulted in December 2021, noted that "*patients would receive care in the community, mostly from district nurses for dressings and palliative care nurses for pain and other symptom management. These patients are poorly served in the community as their diseases are very morbid and difficult to manage*".

Following application of the decision rules, [redacted] patients receiving platinum-based chemotherapy were included in the integrated chart review cohort for analysis, this included a subset of [redacted] audited patients.

A summary of baseline characteristics for the integrated chart review, EMPOWER-CSCC 1 and Study 1423 trials are presented in Appendix A.15.1 (Table 23). Baseline characteristics across the populations are similar with comparable median age (72, 72.5 and [redacted] for EMPOWER-CSCC 1, Study 1423 and the integrated chart review, respectively), proportion of male population (83.4%, 80.8% and [redacted]%), tumour location (predominantly head and neck) and disease severity (59.6%, 61.5% and [redacted]% mCSCC). However, there are notable differences in disease characteristics (i.e., Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), prior systemic therapy, etc.) which limited their inclusion within propensity score models generated as part of evidence synthesis due to poor overlap.

Compared to the Jarkowski 2016 study, which was conducted in the United States the chart review has the advantage that it is in a UK population and collected patient characteristics that are similar to those collected in EMPOWER-CSCC 1, allowing for more prognostic factors to be considered when conducting indirect comparisons and population adjustments (see Section A.7.1 and Appendix A.15.8).

A.6.2.2 Survival outcomes

Overall survival (OS)

The outcome of interest for the integrated chart review analyses was OS, defined as time from initiation of treatment to death, which is aligned with EMPOWER-CSCC 1. Median OS observed in the chart review was ~15 months (n =) similar to that reported by Jarkowski 2016 (15.1 months). Figure 4 presents the OS data from the integrated chart review and Jarkowski 2016.

Figure 4: Comparison of overall survival estimates from the UK chart review (integrated data [n=]), and the comparator data

Overall, the retrospective chart review demonstrates that survival outcomes for patients in the UK on platinum-based chemotherapy are very low; expected median OS is less than 2-years. In contrast, data from EMPOWER-CSCC 1 shows benefits in OS, with median OS yet to be reached at the July 2021 DCO (maximum follow-up of months), in addition to its favourable safety and tolerability profile. As such, treatment with platinum-based chemotherapy would now be considered an inferior therapy for this patient population, a view supported by clinical opinion during an advisory board conducted in December 2021 (see Appendix A.15.15).

Progression-free survival (PFS)

The majority of the PFS events in the chart review were deaths ([redacted] out of [redacted] PFS events, N at risk = [redacted]), which indicated that progression events were likely unrecorded or missing from the chart review data. The PFS data reported as part of the chart review was not considered reliable and for this reason a comparison was not conducted. Instead, PFS for the analysis is informed by Jarkowski et al. 2016. This was considered appropriate given the similarities observed in OS outcomes between the two studies (see Figure 4) and that Jarkowski remains the most robust source of comparator data for PFS in CSCC.

A.6.3 Jarkowski et al. 2016

In this retrospective study, records were obtained and reviewed for all patients diagnosed with CSCC from January 2001 through January 2011 using an electronic cancer database and infusion centre appointment records. Aggregate data from this study was used as the primary source of comparator data in TA592.

Due to the lack of reliable PFS data collected in the chart review, data from the Jarkowski 2016 study is used to inform the economic evaluation base case. Data for PFS is presented in Figure 5, which shows that PFS is lower in Jarkowski 2016 than in the cemiplimab trials. The OS data from Jarkowski 2016 is shown in Figure 6 (used in scenario analysis).

Figure 5: Kaplan-Meier data for progression-free survival from Jarkowski 2016 and Cemiplimab trials

A.6.4 Sun et al. 2019

The company submission for TA592 did not identify published data to inform the comparator arm for BSC. BSC is an important comparator for cemiplimab; however, clinical opinion suggests many patients receiving BSC are treated in the community and so limited published data are available. Therefore, the TA592 submission used Jarkowski 2016 (n = 25; including 18 patients receiving platinum-based chemotherapy regimens) to inform BSC. At the time this was deemed a very conservative approach; due to the high proportion of patients treated with chemotherapy in the study, and likely to provide ICERs which are not truly reflective of the comparison to effective treatment with cemiplimab.

During the TA592 appraisal process the ERG identified Sun 2019; a newly published retrospective study reporting aggregate level survival outcomes in patients with advanced CSCC receiving BSC.[3] NICE clinical experts noted that this would be a more appropriate source of BSC data than using Jarkowski 2016.[6]

Sun, 2019 evaluated 72 patients with CSCC of the head and neck, of which, nine patients underwent salvage surgery +/- postoperative radiotherapy, 36 patients had

unresectable lesions and 27 patients did not have data on their salvage therapies. Additionally, 40 out of 72 patients (55.6%) were immunosuppressed. Of the 36 patients with unresectable lesions, they either received palliative radiotherapy (n = 21), palliative chemotherapy (n = 4), cetuximab (n = 2), or were transferred to hospice care with no further therapy (n = 9). Data for the 36 unresectable patients were presented by immune status. As immunocompromised patients would have been excluded from the cemiplimab trials, only data for immunocompetent patients (n = 20) was included for comparison to BSC. This subset matches the patients who would have been eligible for treatment with cemiplimab.

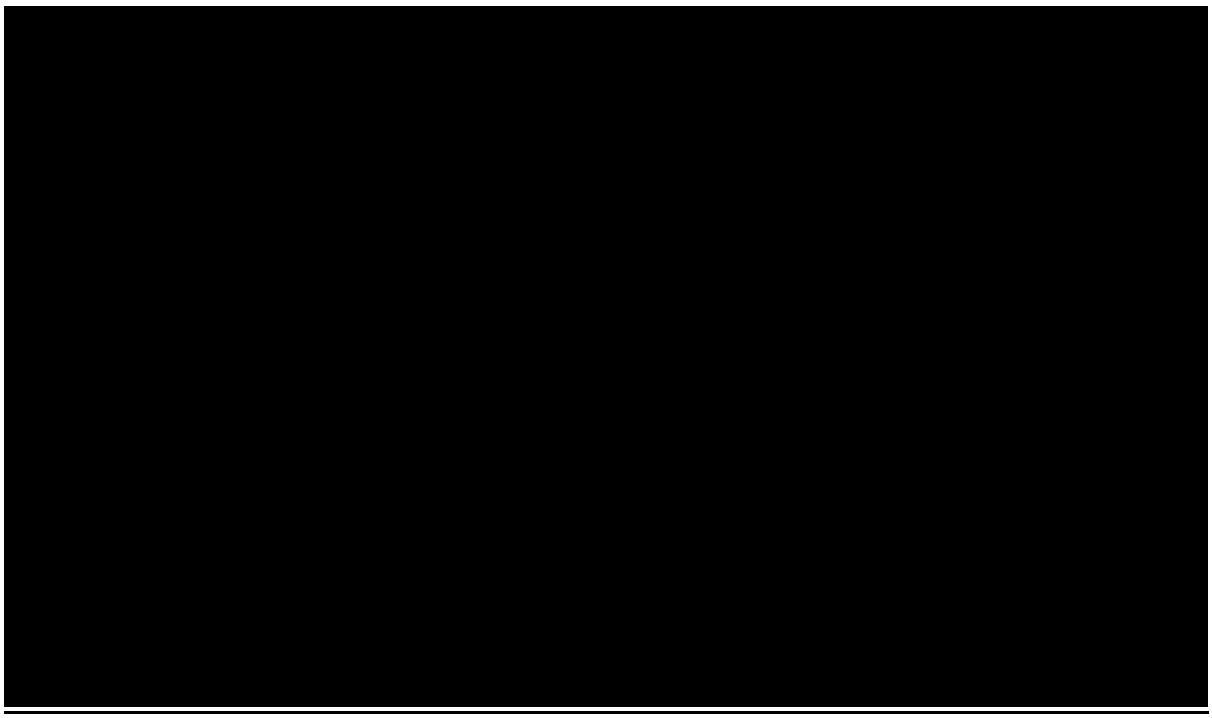
Patient characteristics were not reported for the 36 unresectable patients or for the 20 patient immunocompetent subset. However, patient characteristics were reported for the 32 immunocompetent patients overall, this included the 20 patients of interest who had unresectable lesions plus those who either were resectable or whose status was unknown. To be able to conduct population adjustments for comparisons to cemiplimab the analysis assumes the distribution of characteristics in the 32 immunocompetent patients overall were approximately the same as those for the 20 unresectable, immunocompetent patients of interest.

The population reported in Sun 2019 (Appendix A.15.1, Table 23) are generally similar to the cemiplimab trials in terms of the general patient demographics (predominately male population, median age of 73 years vs. 72 years in cemiplimab trials) and proportion of patients with mCSCC. However, there were differences in performance status with immunocompetent patients by Sun 2019 presenting with ECOG PS 0-2 (Karnofsky Performance Status 60-90) vs ECOG 0-1 in the cemiplimab trials. Additionally, all patients had received prior surgery and postoperative radiotherapy in Sun 2019, as per eligibility criteria, which was not the case for the cemiplimab trials.

The median OS reported by Sun 2019 for the 20 immunocompetent patients with unresectable lesions receiving BSC was 5 months (Figure 6). During the TA592 appraisal process, clinical experts considered Sun 2019 a more reasonable estimate of OS associated with BSC, compared with Jarkowski 2016 (median OS of 15.1 months). The survival estimates reported by Sun 2019 demonstrate that advanced CSCC patients receiving BSC have very low survival estimates (less than 1 year).

PFS was not reported by Sun 2019, it is assumed patients receiving palliative care have no further treatment options available.

Figure 6: Kaplan–Meier curves for overall survival for Best Supportive Care from published studies and EMPOWER-CSCC 1 (July 2021)



A.6.5 Cemiplimab Systemic Anti-Cancer Therapy (SACT) dataset cohort

NHS England Digital provided an aggregate level summary report of the 352 patients who were included in the systemic anti-cancer therapy (SACT) cohort for treatment with cemiplimab between 2 July 2019 and 1 March 2021. Median follow-up was 10.2 months (6.3 – 21.9 months), compared to median follow-up of [redacted] months from EMPOWER-CSCC 1 (maximum follow-up of [redacted]-month). Relative to EMPOWER-CSCC 1, the SACT data set is immature and should be reviewed with this in mind.

A summary of patient characteristics included in the SACT cohort is presented in Appendix A.15.1 (Table 23). Clinical experts consulted have suggested that the baseline characteristics of the UK population that will receive cemiplimab are generally aligned with the patients within EMPOWER-CSCC 1. However, in comparison to EMPOWER-CSCC 1, the SACT dataset represents a frailer, older population; the median age of the SACT dataset was higher (median age 77 years vs. 72 years) and a higher percentage of patients had an ECOG PS score ≥ 1 or

their ECOG PS was missing: ECOG PS score of 0 (18% vs 44.6%), 1 (63% vs 55.4%), 2 (4% vs 0%) or missing (14% vs 0%) for the SACT data vs EMPOWER-CSCC 1 study respectively.

The median treatment duration for patients (n = 352) in the SACT cohort was 8 months (95% CI: 6.2, 9.3). At 6 months, 57% of patients were still receiving treatment (95% CI: 51%, 62%), 39% of patients were still receiving treatment at 12 months (95% CI: 51%, 62%) and 33% of patients were still receiving treatment at 18 months (95% CI: 26%, 39%). However, the SACT data is not mature enough to see the impact of the 2-year stopping rule on continued treatment benefit, which was one of the considerations raised in the MAA.

Figure 7 presents the KM plot for OS; censored at 6 September 2021, the median OS was 21 months and Table 8 shows the associated numbers at risk. Survival at 6 months was 75% (95% CI: 70%, 79%), at 12 months, survival was 63% (95% CI: 58%, 68%), at 18 months survival was 56% (95% CI: 49%, 61%) and at 24 months, survival was 46% (95% CI: 37%, 54%). In contrast, EMPOWER-CSCC 1 had yet to reach median OS at the July 2021 DCO ([redacted]% alive at [redacted] months). The observed difference in OS may be due to several reasons including the older and sicker population (more ECOG PS ≥ 1 patients), and fewer/no patients having had prior treatment (itself suggesting a frailer population with reported PS 1) recruited in SACT compared to EMPOWER-CSCC 1. In addition, 8 months after the entry of cemiplimab to the CDF, the COVID-19 pandemic began, though there has not been an impact on the data collection process, there will likely have been an impact in clinical presentation and treatment pathways as a result of the pandemic.

Figure 7: Kaplan–Meier survival plot for patients receiving cemiplimab in the SACT database cohort (N = 352)

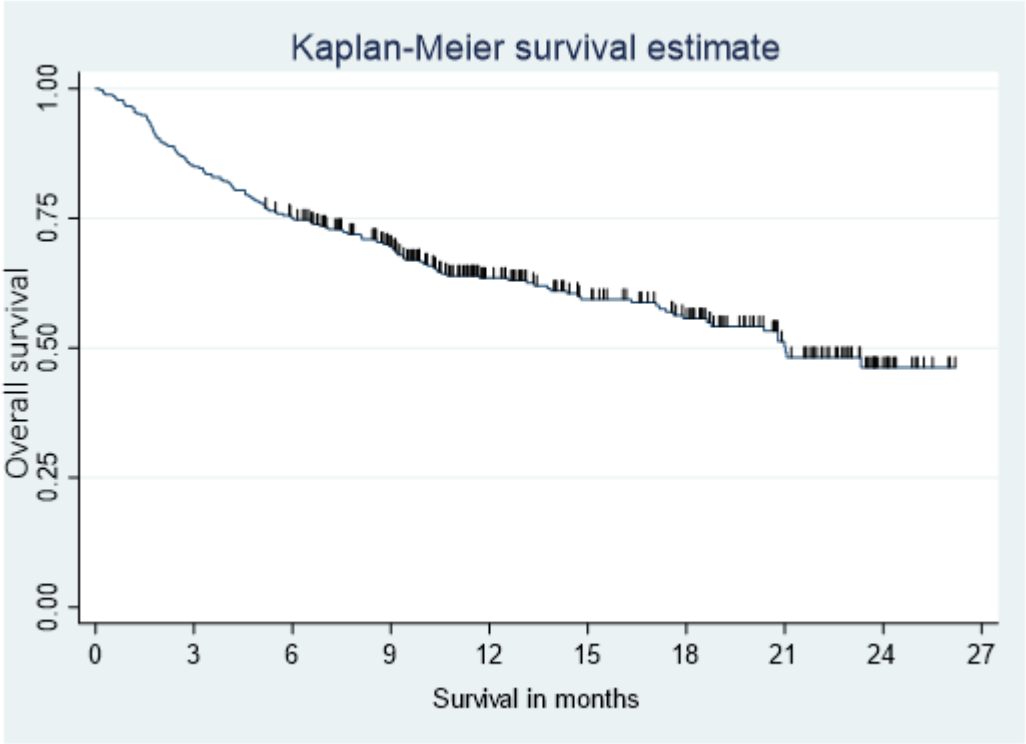


Table 8. Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-27	3-27	6-27	9-27	12-27	15-27	18-27	21-27	24-27
Number at risk	352	299	259	207	141	107	85	49	12

It is worth noting that EMPOWER-CSCC 1 did not include patients with PS > 1, however within SACT 4% of patients were reported to have PS 2, and 14% had missing data. Within an aged cohort clinical experts have suggested ECOG PS is somewhat biased in itself and these patients may in fact have poorer PS. Adjustment for these factors when comparing to EMPOWER-CSCC 1 is likely to have an impact on the outcomes reported by SACT.

Furthermore, clinical experts consulted have suggested that there are challenges in using ECOG PS to assess performance status in older patients. Clinicians suggested that assessors unconsciously compensate for age and frailty when assessing elderly patients; according to the tool a PS 1 patient aged 80 years is

deemed the same as one aged 40 years. However, this is rarely the case, with compensations made for the comorbidities and frailty of the 80-year-old relative to their peers, not to other patients being assessed. This would suggest that older patients with PS 1 would in fact have worse PS values if their assessment was blinded to age -related frailty and comorbidities. Clinicians suggested that it was likely that patients captured in SACT may have poorer PS than recorded. Clinicians consulted also confirmed that in practice they are using cemiplimab to treat an older patient population; with some patients well into their 90's, given cemiplimab's good tolerability profile.

Clinical experts have suggested that only younger fitter patients would be able to tolerate traditional platinum-based chemotherapy regimens. Given the older age and poorer performance status of the patients in the SACT cohort, were cemiplimab not available it is likely that a large proportion of these patients would have received BSC as they would not be able to tolerate traditional platinum-based chemotherapy regimens. Clinical opinion suggests that patients receiving BSC would not be expected to survive beyond 6 months. Due to the advantages associated with cemiplimab in terms of its tolerability and safety profile, these patients are now able to receive cemiplimab which may offer an improvement to the PS of patients and as shown by the SACT data result in improved survival.

Immunocompromised patients were excluded from EMPOWER-CSCC 1, however in SACT, 4% of patients had previous solid organ transplant or autoimmune disease. This data is however incomplete as no data on this characteristic was reported for 7% of patients.

Clinical expert opinion also suggested that the proportion of patients with prior systemic therapy in EMPOWER-CSCC 1 and Study 1423 (37% of 219 patients received prior systemic therapy) is higher than would be observed in clinical practice, suggesting that the trial population may be fitter compared to the SACT cohort.

The data collection period for SACT coincided with the COVID-19 pandemic which may also have implications for interpretation of the data. Clinical experts noted a drop in referrals during the early period of the pandemic with patients subsequently presenting with more advanced disease, which may have had an impact on

assessment, treatment options and outcomes. Some clinical experts also reported that COVID-19 led to extended dosing intervals and missed doses of cemiplimab.

Data from SACT is short term, in some instances incomplete and contains a number of uncertainties compared to EMPOWER-CSCC 1, therefore use of the longer-term trial data is preferred. A scenario analysis utilizing SACT baseline characteristics (age and gender) is provided to explore the impact of SACT population characteristics.

A.6.6 Summary of evidence and use within the submission

A summary of evidence sources used to inform the submission are presented in Table 9.

Table 9: Evidence sources used to inform submission and rationale for inclusion/exclusion

Study	Intervention	Use within submission	Rationale for use/ exclusion
Pooled Study 1423 and EMPOWER CSCC-1	Cemiplimab	Primary source of data for cemiplimab within the economic evaluation and assessment of long-term survival	Provides [redacted] months survival data ([redacted] months of follow up)
SACT dataset	Cemiplimab	Baseline characteristics explored as a scenario analysis within the model	Understand impact considering the different baseline characteristics observed within the dataset compared to EMPOWER-CSCC-1 Excluded as primary source in favour of more robust longer term trial data
UK cohort retrospective chart review	Platinum-based chemotherapy	Inform OS data for comparator arm within the model.	Reflects UK clinical practice, addresses concern over generalisability of comparator dataset used in TA592
Sun et al 2019	BSC	Inform OS for BSC	Primary source of data for BSC patients.
Jarkowski et al. 2016	Platinum-based chemotherapy	Inform PFS data for comparator arm within the model	Robust source of PFS, which is not available within the retrospective chart review or Sun et al.

			Excluded as primary source for OS, due to non-UK patients, lack of chemotherapy treatment and small sample size

BSC, Best supportive care; OS, Overall survival; PFS, Progression-free survival; SACT, Systemic anti-cancer therapy; TA, Technology appraisal; UK, United Kingdom.

A.7 Evidence synthesis

The chart review described in Section A.6.2, aimed to provide data to estimate a comparative platinum-based chemotherapy treatment arm for patients with advanced CSCC in UK clinical practice. However, because patients were not randomised to receive cemiplimab or platinum-based chemotherapy, a simple comparison of the outcomes with the two treatments is at substantial risk of bias. To address this, a population-adjusted indirect comparison was conducted using individual patient level data (IPD) from the cemiplimab trials: Study 1423 (April 2019 DCO, n = 26) and EMPOWER-CSCC 1 (July 2021 DCO, n = 193) and the integrated chart review cohort (n = [redacted]) for platinum-based chemotherapy to estimate OS benefit. Further details are provided in Section A.7.1.

To estimate survival benefits for the platinum-based chemotherapy and BSC comparator arms, simulated treatment comparisons were conducted using data from Jarkowski 2016 and Sun 2019, respectively and the cemiplimab trials. Further details of the conducted ITC are described in Section A.7.3.

As previously stated, PFS data from Jarkowski 2016 is used as a measure of PFS efficacy for the analyses using the integrated chart review and the BSC analysis using Sun 2019 assumes patients are within the post-progressive state.

A.7.1 Indirect treatment comparison – Platinum Based Chemotherapy (Retrospective Chart Review)

Recommended methodologies for adjustment of data as outlined in the NICE technical support document (TSD) 17 were considered (see Appendix A.15.8 for detail of recommended methodologies).[7] Following consideration of each methodology, propensity score-based inverse probability weighting (IPW) was conducted to estimate the treatment effect that would have been observed had the

chart review patients been observed in the EMPOWER-CSCC 1/Study 1423 trial; analogous to 'average treatment effect in the treated' (ATT) methodology.

Propensity scores were derived using logistic regression where the outcome was treatment (membership of EMPOWER-CSCC 1/Study 1423) and defined as the predicted probability of treatment based on relevant covariates. The covariates (prognostic factors) were identified through a targeted literature review and validated by clinical expert opinion.[8] Propensity scores were used to generate a weight for each patient, and these were used to re-weight the chart review population to obtain a treatment effect in a sample similar to the treated population by up-weighting patients who are more similar to the EMPOWER-CSCC 1/Study 1423 patients and down-weighting patients who are dissimilar. In the presence of extreme weights, trimmed weights, capping the value at the 95th percentile, were applied to reduce the variability of estimated treatment effects.[9] (see Appendix A.15.8 for more detail on covariate selection, inclusion in the models and weights).

ATT models with varying inclusion of prognostic factors were considered. Prior systemic therapy and Radiation Therapy were not included in any of the ATT propensity score models given the variables had insufficient overlap. ECOG status also had insufficient overlap and was not included in all models; however, given the prognostic importance of ECOG status, this variable was included in the full ATT propensity score model. The extent of the difference for each of the variables was assessed using the standardized differences method and measures were used to identify which model had the best overall improved balance of key covariates (outlined in Appendix A.15.8).[9] The plot of absolute standardized difference for unweighted data, weighted data, and data with trimmed weights (capping the value at the 95th percentile) were used to assess the impact of extreme weights and select the final propensity score model with weights that resulted in the best balance of the key relevant covariates.

Use of the ATT approach and the analysis outcomes relative to other approaches was validated by clinical experts during an advisory board. Sensitivity analyses were conducted matching the trial data to the integrated chart review data (average treatment effect in the controls model (ATC)). However, clinical experts suggested that the extrapolations generated for cemiplimab using this methodology

underestimated its OS benefit; clinicians expected to see plateauing of the benefit at 40-50% between 60 and 120 months. Further details can be found in Appendix A.15.8. [5]

Results

Results of the full model and the two best fitting models for the IPW ATT, including prognostic factors considered are presented in Table 10. The point estimates of the HRs are similar for the models. The results show that excluding patients with extreme weights (trimmed analysis) did not influence the hazard ratios (HRs) for OS substantially and improved the effective sample size (ESS); the adjustment of the sample size that accounts for the weighting of the observations. Based on this, the results of the trimmed IPW analyses were used in the cost-effectiveness model.

The adjusted ATT propensity score model 1 was the best fitting (balancing model) and used in the model base case analysis. As this model does not include ECOG status, the full propensity score model is presented as a scenario analysis for the economic analysis.

Table 10: Overview of ATT analyses included in CE model

	Adjusted chart review (based on cemiplimab population)		
	Full ATT	**ATT model 1**	**ATT model 2**
HR[a] (95% CI)			
HR[a] (95% CI) trimmed			
Balance[b]			
ESS			
ESS trimmed[c,d]			
Characteristic incorporated			
Disease severity			
Age			
Gender			
Differentiation			
Tumour location			
T stage			

ECOG performance status	[redacted]	[redacted]	[redacted]
Prior systemic therapy	[redacted]	[redacted]	[redacted]
Prior radiation	[redacted]	[redacted]	[redacted]

Notes: a) hazard ratios (HR) are cemiplimab vs chemotherapy; b) balance was based on the not-trimmed results; c) ESS is equal to the number of patients after reweighting for the trial for ATC analyses and for the chart review for ATT analyses; d) trimmed patients were not excluded, however, their weight was set at the weight observed at the 95th percentile. **Abbreviations:** ATT, average treatment effect of the treated; CI, confidence interval; ESS, effective sample size; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck; HR, hazard ratio; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; N, no; NP, not possible; T (TNM), T stage of the TNM Classification of Malignant Tumours; Y, yes.

Unadjusted and reweighted patient characteristics in the ATT analyses for the adjusted full ATT model and adjusted ATT model 1 are presented in Table 11. There is still an observed difference between the reweighted chart review patients compared to the cemiplimab trial patients. This may be due to some covariates not being incorporated in the ATT analyses (prior systemic therapy was not included in either model and ECOG PS was not included in ATT model 1) which may be indicative of survival, but could not be incorporated due the data limitations.

Table 11: Unadjusted and reweighted baseline patient characteristics

Characteristic		Chart review (unadjusted)	Chart review (reweighted - full ATT model)	Chart review (reweighted - ATT model 1)	Cemiplimab trials[a]
N[b]		[redacted]	[redacted]	[redacted]	219.0
Disease severity, n (%)	**laCSCC, n (%)**	[redacted]	[redacted]	[redacted]	88.0 (40.2)
	mCSCC	[redacted]	[redacted]	[redacted]	131.0 (59.8)
Age, mean (sd)		[redacted]	[redacted]	[redacted]	71.2 (11.2)
Gender, n (%)	**Male**	[redacted]	[redacted]	[redacted]	182.0 (83.1)
Differentiation, n (%)	**Well**	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate/Poor/ Undifferentiated	[redacted]	[redacted]	[redacted]	[redacted]
	Undetermined	[redacted]	[redacted]	[redacted]	[redacted]
Tumour location, n (%)	**Head and Neck**	[redacted]	[redacted]	[redacted]	[redacted]
	Trunk	[redacted]	[redacted]	[redacted]	[redacted]
	Extremities	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic		Chart review (unadjusted)	Chart review (reweighted - full ATT model)	Chart review (reweighted - ATT model 1)	Cemiplimab trials[a]
T stage (TNM), n (%)	T0	[redacted]	[redacted]	[redacted]	[redacted]
	Tx	[redacted]	[redacted]	[redacted]	[redacted]
	T1	[redacted]	[redacted]	[redacted]	[redacted]
	T2	[redacted]	[redacted]	[redacted]	[redacted]
	T3	[redacted]	[redacted]	[redacted]	[redacted]
	T4	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)	0	[redacted]	[redacted]	[redacted]	96.0 (43.8)
	1	[redacted]	[redacted]	[redacted]	123.0 (56.2)
Prior systemic therapy, n (%)		[redacted]	[redacted]	[redacted]	80 (36.5)
Prior radiation, n (%)		[redacted]	[redacted]	[redacted]	[redacted]

Notes: a) EMPOWER-CSCC 1 and Study 1423 pooled; b) for the adjusted models N is equal to the sum of weights. **Abbreviations:** ATT, average treatment effect on treated; ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; NA, not applicable; sd, standard deviation; T (TNM), T stage of the TNM Classification of Malignant Tumours.

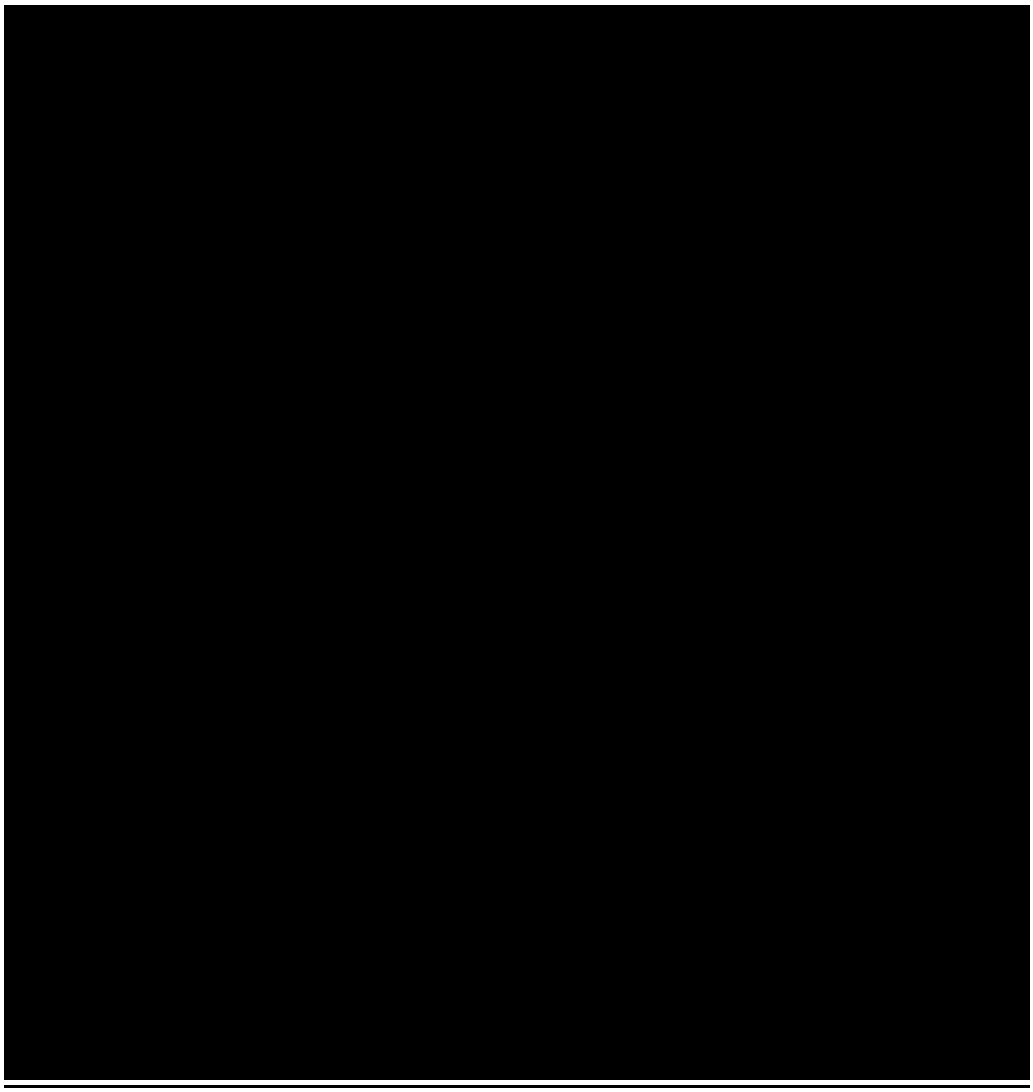
The KM plots for the naïve, weighted and trimmed results for model 1 of the ATT analyses are presented in Figure 8. For completeness, the KM plots for the full ATT is presented in Appendix A.15.8, and an overview of the ATT analyses are presented in Table 28.

The results of the analysis indicate a statistically significant benefit with cemiplimab versus platinum-based chemotherapy in patients with advanced CSCC: the 95% CIs (see Table 10) indicate that cemiplimab is beneficial (the upper bound is <1 for the IPW models).

The analysis of the integrated chart review data further highlights that cemiplimab provides greater treatment benefit for the patient population than treatment with platinum-based chemotherapy.

The results of the sensitivity analyses conducted matching the trial data to the integrated chart review data (ATC) are largely consistent and are presented in Appendix A.15.8.

Figure 8: Kaplan–Meier curves full ATT model 1: weighted (above) and trimmed (below)



Abbreviations: *ATT average treatment effect of the treated; NA, not applicable; PBC, platinum-based chemotherapy.*

A.7.2 Indirect treatment comparison – Platinum Based Chemotherapy (Jarkowski 2016)

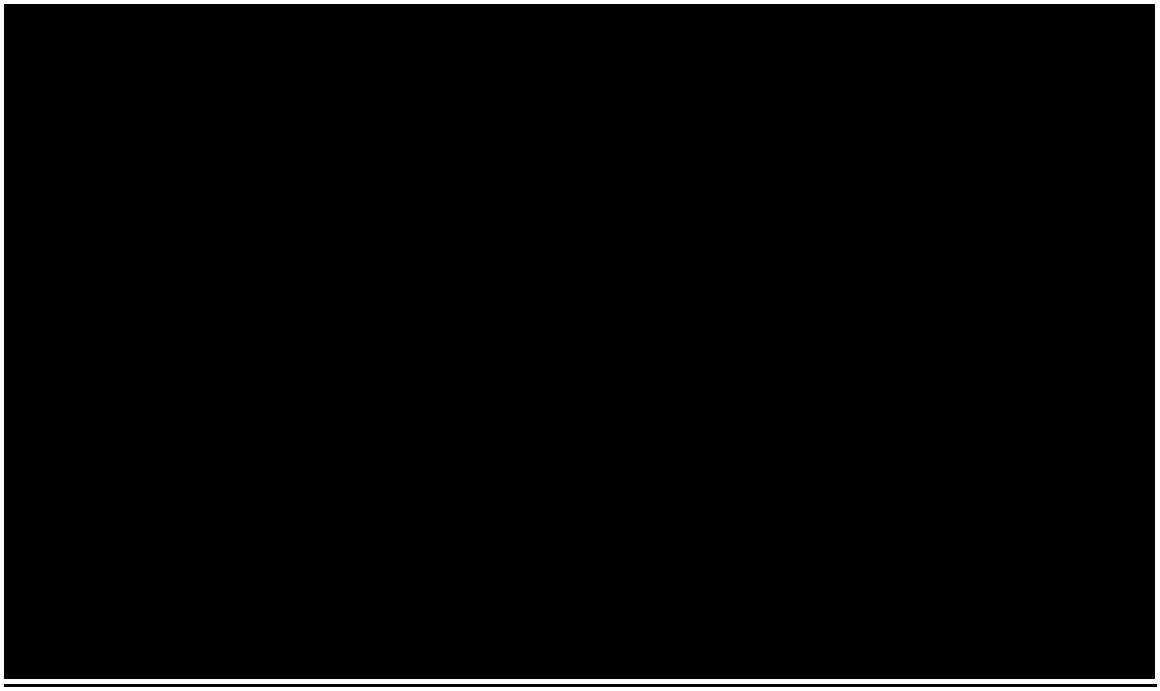
A simulated treatment comparison (STC) and matching-adjusted indirect comparison (MAIC) were conducted to adjust for the difference in baseline patient characteristics to generate estimates of PFS and OS. Details of each method are outlined in Appendix A.15.8. Relative treatment effects were estimated as HRs by means of Cox regression.

STCs may offer some advantages over MAICs for population adjustments: the risk of bias may be less for this approach when the model is misspecified (either outcome regression or propensity score model), although estimates of precision may be overestimated. Additionally, NICE recommends that the ESS is reported in MAICs. In the current context where the cost-effectiveness model for this study requires survival estimates to be extrapolated to a lifetime horizon (i.e. 30 years), changes in KM curves due to reweighting may have profound implications for cost-effectiveness results. Like NICE TA592, the STC was selected as the base case analyses whilst the MAIC was performed as a sensitivity analyses. In the base case, only PFS data from Jarkowski 2016 was used, with OS used in sensitivity analysis.

Results OS

For comparisons of OS using pooled EMPOWER-CSCC 1 and Study 1423, the best fitting models in terms of Akaike information criteria (AIC) was the core model. The results of the indirect treatment comparison (ITC) showed cemiplimab is more efficacious than platinum-based chemotherapy across all three methods used (naïve, STC and MAIC) with similar hazard ratios across all methods [redacted])] respectively. Predicted OS from the best fitting models using both the STC and MAIC are presented in Figure 9 and show that the adjustments led to upward shifts in the cemiplimab curve, indicating better survival for cemiplimab compared to platinum-based chemotherapy. Note, the results of the MAIC should be interpreted with caution as weights are not always well distributed for this analysis.

Figure 9: Unadjusted and population-adjusted Kaplan–Meier curves for overall survival with cemiplimab (pooled EMPOWER-CSCC 1/Study 1423) overlaid with observed curve for chemotherapy with platinum from Jarkowski et al. 2016



Results PFS

The core model was the best fitting model for PFS. Figure 10 presents the PFS from the best fitting models using both the STC and MAIC. For PFS, though point estimates are in favour of cemiplimab, cemiplimab is comparable to Jarkowski 2016 using all three methods as the KM curves for cemiplimab and platinum-based chemotherapy cross at ~ 44 months, with reported hazard ratios for the naïve, STC and MAIC analyses of [redacted] respectively.

Figure 10: Unadjusted and population-adjusted Kaplan–Meier curves for overall survival with cemiplimab (pooled EMPOWER-CSCC 1/Study 1423)

overlaid with observed curve for chemotherapy with platinum from Jarkowski et al. 2016

A.7.3 Indirect treatment comparison – Best supportive care (Sun et al. 2019)

A simulated treatment comparison (STC) and matching-adjusted indirect comparison (MAIC) were conducted to adjust for the difference in baseline patient characteristics to generate estimates of OS. Details of each method are outlined in Appendix A.15.9. Relative treatment effects were estimated as HRs by means of Cox regression.

Results

For comparisons of OS using pooled EMPOWER-CSCC 1 and Study 1423, the best fitting models in terms of Akaike information criteria (AIC) was the extended model. The findings demonstrate that cemiplimab is more efficacious across all three methods used (naïve, STC and MAIC) with similar hazard ratios across all methods . Predicted OS from the best fitting models using both the STC and MAIC are presented in Figure 11 and show that the STC population adjustment led to upward shifts in the cemiplimab

curve, indicating better survival for cemiplimab compared to best supportive care. Note, the results of the MAIC should be interpreted with caution as weights are not always well distributed for this analysis.

Figure 11: Unadjusted and population-adjusted Kaplan–Meier curves for overall survival with cemiplimab (pooled EMPOWER-CSCC 1/Study 1423) overlaid with observed curve for best supportive care from Sun et al. 2019 (MAIC ESS n = [redacted])

A.8 Incorporating collected data into the economic evaluation

The economic evaluation compares cemiplimab to platinum-based chemotherapy and BSC. In the base case analysis, cemiplimab survival (OS and PFS) is informed by the EMPOWER-CSCC 1 and Study 1423 trials. OS for the platinum-based chemotherapy comparator arm is informed by the retrospective chart review and OS for the BSC comparator arm is informed by Sun 2019. As the PFS data collected as part of the chart review was not deemed reliable (see Section 0), PFS data from Jarkowski 2016 was used to inform PFS for platinum-based chemotherapy as the OS data in both studies shows similar trends. Sun 2019 did not report PFS,

therefore, BSC patients are assumed to be palliative in nature and patients enter the cost-effectiveness model in a post-progression health state.

A.8.1 Endpoints included in the analysis

To support the updated economic analysis and reduce uncertainty, the endpoints outlined in Table 12 were analysed and included in the cost-effectiveness model:

Table 12: Data used in economic analysis

Treatment	Submission	OS	PFS
Cemiplimab	**TA592**	EMPOWER-CSCC 1, October 2017 data cut	EMPOWER-CSCC 1, October 2017 data cut
	Post-CDF submission	EMPOWER-CSCC 1, July 2021 data cut	EMPOWER-CSCC 1, July 2021 data cut
Platinum-based chemotherapy	**TA592**	Naïve comparator data (Jarkowski et al., 2016)	Naïve comparator data (Jarkowski et al., 2016)
	Post-CDF submission	UK Chart review IPW ATT analysis, model 1	Jarkowski et al. 2016, STC analysis
BSC	**TA592**	Naïve comparator data (Jarkowski et al., 2016)	Naïve comparator data (Jarkowski et al., 2016)
	Post-CDF submission	Sun et al. 2019, STC analysis	N/A, BSC assumed to be palliative in nature and patients enter the model in post-progression health state

ATT, average treatment effect of the treated; BSC, Best supportive care; CDF, Cancer drugs fund; IPW, inverse probability weighting; STC, Simulated treatment comparison; TA, Technology appraisal; UK, United Kingdom.

A.8.2 Analysis methodology

As a lifetime time horizon is required for the for the partitioned survival approach, it was necessary to extrapolate available data until all patients have progressed or died. The same modelling approach as TA592 was used, where each intervention was modelled independently for both PFS and OS with alternative parametric models were fit to all available data. The proportional hazards assumption was tested for completeness. Details of the log-cumulative hazard plots are provided in Appendix A.15.2 which confirm that it is appropriate to extrapolate OS outcomes based on individually fitted curves for each trial arm.

The following parametric survival distributions were estimated for PFS and OS: Weibull (p1 = 0), Gompertz (p1 = 1), second-order fractional polynomials (FPs) with power p1 = 0 or 1 and power p2 = -1, -0.5, 0, 0.5, or 1, log-normal and log-logistic distributions.

Following NICE DSU TSD 14 and 21 guidance, the survival models were assessed for suitability considering:

- Visual fit to the observed KM data within the trial period for EMPOWER-CSCC 1 (Appendix A.15.2 and A.15.3)
- Assessment of the shape of hazard over time for cemiplimab and comparators (Appendix A.15.2 and A.15.3)
- Statistical goodness of fit indicated by AIC and Bayesian Information Criterion (BIC) values (Appendix A.15.4)
- Clinical validation of the curves (Appendix A.15.15).[5]

A.8.3 Results OS

Table 13 presents a summary of OS model settings used during TA592.

Table 13: Curve selection for Overall Survival in TA 592

Comparator	Overall Survival	Curve selection	Rationale
Cemiplimab	EMPOWER-CSCC 1, October 2017 data cut	Log Normal distribution	Best fitting and clinical validation
Platinum-based chemotherapy	Naïve comparator data (Jarkowski et al., 2016	Gompertz distribution	Best fitting and clinical validation
Best supportive care	Naïve comparator data (Jarkowski et al., 2016	Gompertz distribution	Conservative assumption

A.8.3.1 Cemiplimab (EMPOWER-CSCC 1) OS results

The log-normal extrapolation was used in the TA592 Company submission model. With the latest observed EMPOWER-CSCC 1 data (maximum [redacted] months follow-up), the log-normal distribution was again a good visual fit and showed decreasing hazards over time, in line with the hazard associated with the observed EMPOWER-CSCC 1 data and clinical expectations and provided a plausible long-term survival extrapolation. The log-normal distribution was also the best fitting distribution in

terms of AIC and BIC fit statistics. This was validated by UK clinical experts attending an advisory board.

Figure 12 presents the OS KM from the July 2021 DCO and estimated OS based on the base case parametric distribution (log-normal) fitted to the observed cemiplimab data for the overall population. The extrapolation demonstrates that that the efficacy of cemiplimab is expected to be maintained for the longer-term. This expectation was supported by feedback from clinical experts at the December 2021 advisory board who noted that the observed survival was in line with real world evidence and given the observed maximum [redacted]month follow-up trial data, they would expect survival to plateau given their experience with immunotherapies in other therapeutic areas (also see Section A.8.5). Goodness of fit statistics and OS extrapolations for alternative distributions are presented in Table 24 and Figure 32, respectively.

Figure 12: Overall survival KM vs fitted model (log-normal) for Cemiplimab using EMPOWER-CSCC 1 data, up to 120 months

KM, Kaplan-Meier

A sensitivity analysis using the ATC adjustment methodology will also be provided to explore alternative cemiplimab extrapolations. The best fitting curve was based on

statistical and clinical validation of analysis outputs. Feedback from clinicians during an advisory board suggested that the extrapolations generated by the ATC approach likely underestimated the benefits of cemiplimab.

A.8.3.2 Platinum-Based Chemotherapy (Retrospective Chart Review) OS results

NICE TA592 utilised data from the Jarkowski 2016 study to generate an OS curve for the comparator, platinum-based chemotherapy.

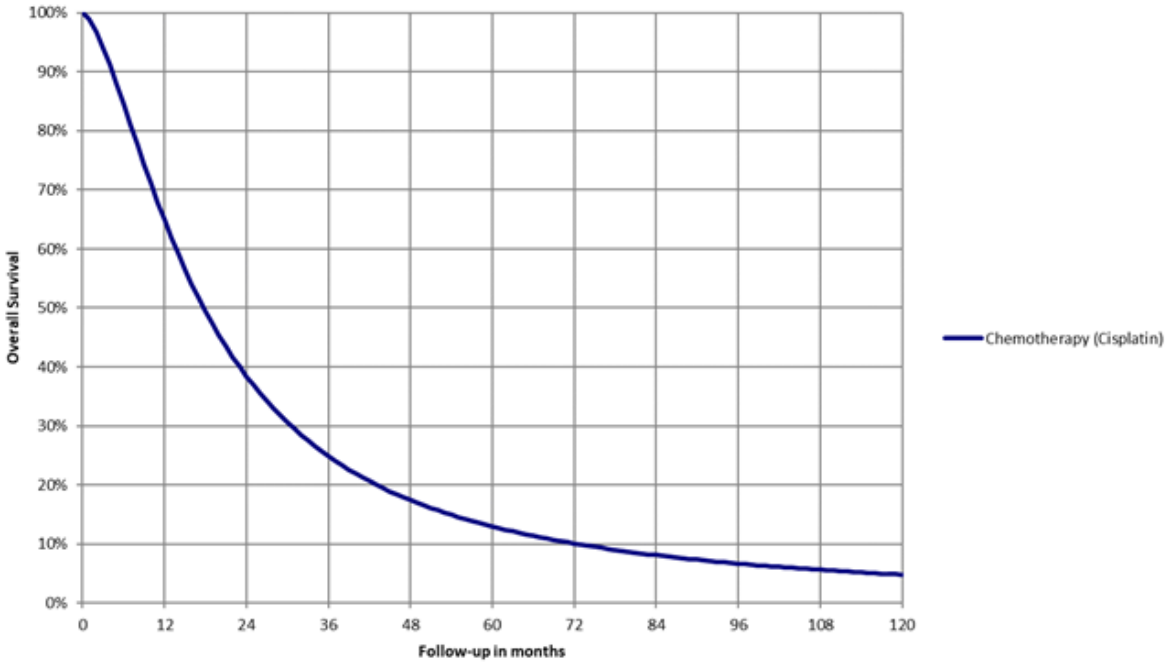
The updated cost-effectiveness analysis utilises OS for the platinum-based chemotherapy comparator generated using data from the ATT analysis of the integrated chart review (see Section A.7.1). AIC/BIC statistics, suggest that the second-order fractional polynomials, p1 = 0 p2 = 0/0.5/1 and p1 = 1 p2 = -1/-0.5/0 offer the best statistical fit to the data.

Feedback from clinical experts during an advisory board suggests that no patients receiving platinum-based chemotherapy would be alive beyond 3-5 years. Distributions which plateaued (i.e., those offering the best statistical fit to the data) were found to not align well with the feedback from clinical experts. Of the distributions which decrease over time, a review of the hazards over time showed the log logistic to be closely aligned with the observed data. The log-normal and P = 0 P = -0.5 also are within the confidence intervals of the data. Of the distributions for which hazards did decrease over time, the log-logistic was selected as the base case.

Figure 13 summarises the estimated OS based on the selected parametric distribution fitted to the retrospective chart review data. Goodness of fit statistics and OS extrapolations for alternative distributions are presented in Table 24 and Figure 37, respectively.

For completeness, analyses using Jarkowski 2016, including alternative OS parametric distributions are included in the model to accommodate scenario analysis.

Figure 13: Overall survival fitted model (log-logistic) for platinum-based chemotherapy using Chart Review integrated audit (n=[redacted]), up to 120 months



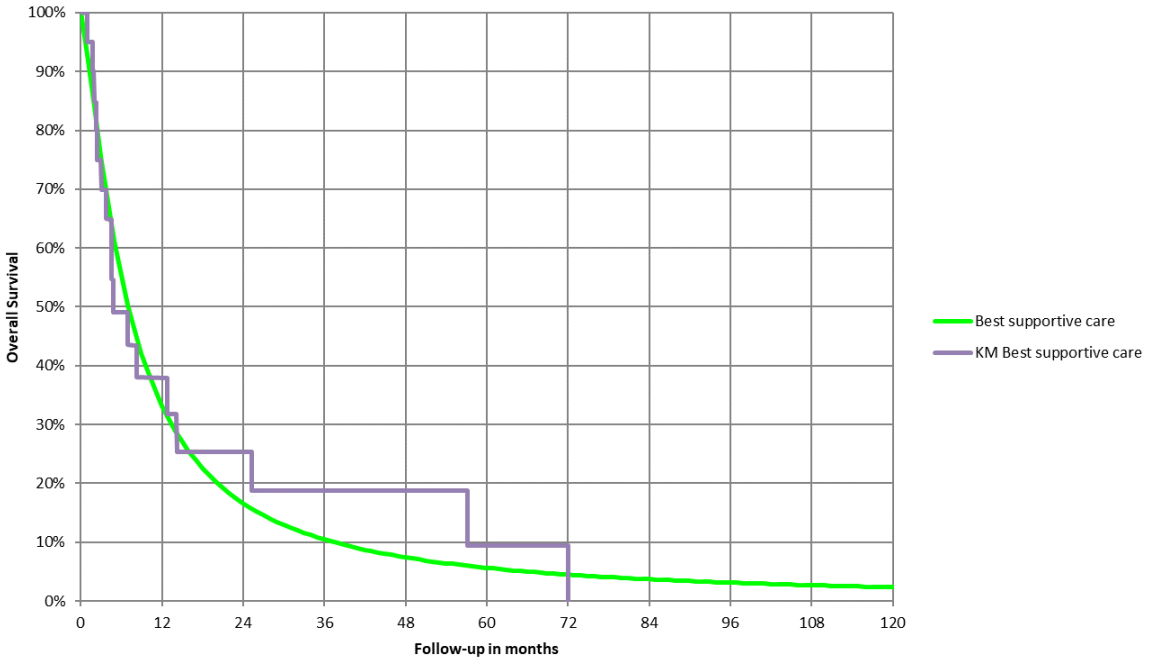
KM, Kaplan-Meier

A.8.3.3 BSC (Sun et al. 2019) OS results

OS estimates were generated using OS data reported for 20 immunocompetent reported by Sun 2019 (see Section A.6.3). The best fitting curves based on AIC/BIC was the second-order fractional polynomial p1= 0 and p2 = -1 (AIC 127.09 and BIC 130.08) and Log-normal (AIC 127.21, BIC 129.21). However, the log-logistic distribution was selected as the most appropriate curve for the analysis as this most closely reflected survival landmarks suggested by expert clinical opinion for patients receiving BSC.

Figure 14 summarises the estimated OS based on the selected parametric distribution fitted to Sun 2019. Goodness of fit statistics and OS extrapolations for alternative distributions are presented in Table 24 and Figure 36, respectively.

Figure 14: Overall survival KM vs fitted model (log-logistic) for BSC using Sun data, up to 120 months



KM, Kaplan-Meier

A.8.4 Results PFS

Table 14 presents PFS model settings used during NICE TA592.

Table 14: Curve selection of PFS in NICE TA 592

	PFS	Curve selection
Cemiplimab	EMPOWER-CSCC 1, October 2017 data cut	Weibull distribution[a]
Platinum-based chemotherapy arm	Naïve comparator data (Jarkowski, 2016	Weibull distribution
BSC arm	Naïve comparator data (Jarkowski, 2016)	Weibull distribution
Key: a) Distribution changed to log-normal during NICE post-submission process		

A.8.4.1 Cemiplimab (EMPOWER-CSCC 1) PFS results

NICE TA592 utilised the Weibull distribution to extrapolate PFS data from the October 2017 DCO. However, within the latest observed EMPOWER-CSCC 1 PFS data (with a maximum of [redacted] months follow-up, July 2021 DCO), this distribution offers the poorest statistical fit (AIC/BIC) to the cemiplimab data.

From a review of the hazard distributions fit to the observed data (Figure 60), the p1 = 1 p2 = 1 seems to fit closely to the tail of the observed data ([redacted]months). However, the PFS KM for cemiplimab drops to zero driven by [redacted]OS events ([redacted]) occurring in the cohort after the end of median PFS follow-up ([redacted]) (see Section A.6.1.3).

Feedback from UK clinical experts at an advisory board suggested PFS was likely to plateau, a maximum of 5-year wait for this plateau could be expected but is likely to be earlier (as observed in melanoma and lung cancer). They suggested use of the 5-year landmark survival was a useful, easy reference point and considered the second-order fractional polynomial with power p1 = 0 p2 = –1 the most relevant curve.

The second-order fractional polynomial with power p1 = 0 p2 = –1 has the best statistical fit (see Table 24) and a plausible extrapolation over time (i.e. decreasing and does not intersect OS). Based on statistical fit, plausibility of extrapolation over time and clinical feedback, this curve was selected for use in the base case.

A.15.3 summarises the estimated PFS based on the selected parametric distribution fitted to the observed cemiplimab data for the overall population. Goodness of fit statistics and PFS extrapolations for alternative distributions are presented in Table 24 and Figure 60, respectively.

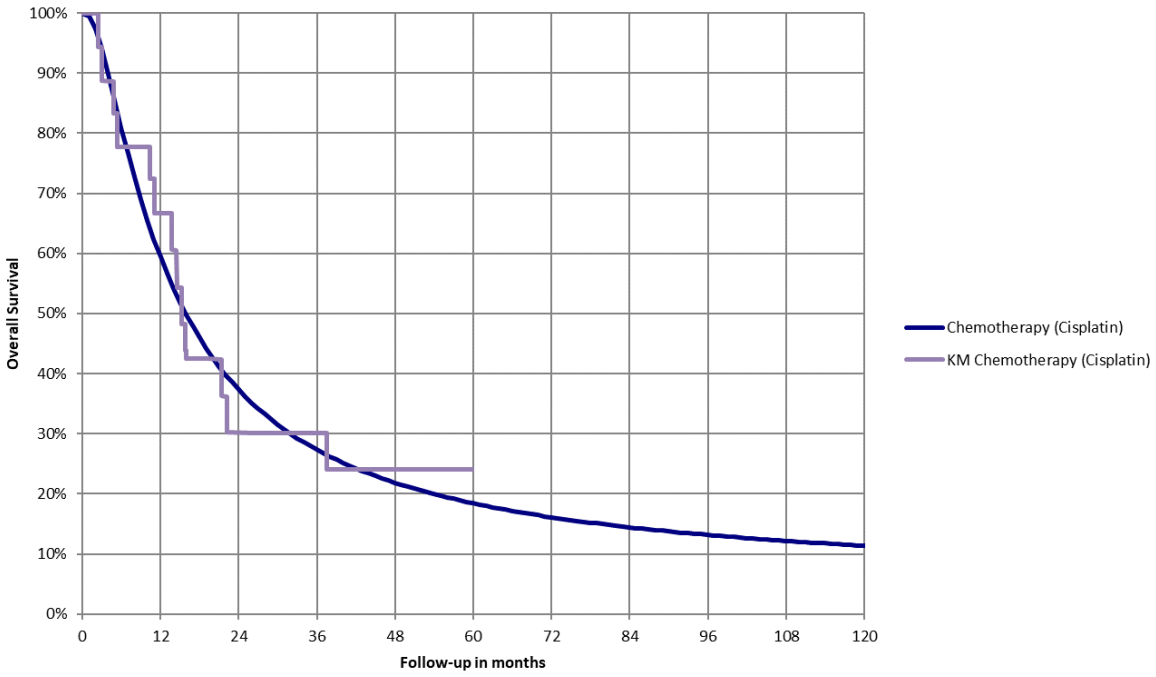
Figure 15: Progression-free survival KM vs fitted model (p1=0, p2=-1) for Cemiplimab using EMPOWER data, up to 120 months

KM, Kaplan-Meier

A.8.4.2 Platinum-Based Chemotherapy (Jarkowski et al. 2016) PFS results

In the Company submission model for TA592 data from Jarkowski 2016 were used to generate comparator curves for chemotherapy and BSC. As PFS from the chart review was not considered sufficiently robust (see Section A.6.2), no changes have been made to the PFS approach in the updated cost-effectiveness analysis, with data from Jarkowski 2016 used to generate comparator curves. The Weibull model that was selected to inform TA592 is maintained for this submission as the best fitting distribution. Figure 16 summarises the estimated PFS based on the selected Weibull parametric distribution fitted to the Jarkowski 2016. Goodness of fit statistics and PFS extrapolations for alternative distributions are presented in Table 24 and Figure 61, respectively.

Figure 16: Progression-free survival KM vs Weibull fitted model for chemotherapy using Jarkowski data, up to 120 months



KM, Kaplan-Meier

A.8.4.3 BSC (Sun et al. 2019) PFS results

Sun 2019 only reported OS data, therefore in the economic analysis all patients were conservatively assumed to start in the post-progression health state as there was insufficient evidence to inform PFS. UK clinical experts consulted by Sanofi considered these to be reasonable approaches in the absence of more robust evidence for BSC.[5]

A.8.5 Continuation of treatment benefit after stopping (treatment waning)

The EMPOWER-CSCC 1 study incorporated a treatment stopping rule where, for a cohort of patients, cemiplimab was administered until progression or a maximum treatment duration of 96 weeks (22 months). The Company submission for NICE TA592 incorporated an assumption to account for potential waning of cemiplimab benefit (in terms of PFS and OS) following the cessation of treatment was applied. The hazards for cemiplimab were assumed equal to those of the comparator from 36 months (i.e., end of follow-up at the October 2017 DCO) until the end of the time horizon of the model.

The final appraisal document (FAD) for TA592 recommended that treatment with cemiplimab be continued until disease progression, toxicity or for up to a maximum of 24 months, whichever is sooner.

Previous health technology assessment (HTA) submissions for pembrolizumab, nivolumab in other tumours with 2-year stopping rules have presented a variety of methodologies to account for continued treatment benefit and treatment waning in their base case or as scenario analyses.[10, 11]

With the updated EMPOWER CSCC 1 data cut, there are now survival data for cemiplimab patients up to the last follow-up (maximum follow-up at [redacted] months) following treatment cessation at 22 months. Therefore, any waning of the treatment effect after stopping treatment should be captured in the data up to [redacted] months, so it would be inappropriate to apply any additional waning of treatment effect before this date.

In the updated analysis, the benefit of cemiplimab is assumed to continue until 60 months (i.e., updated end of study follow-up) at which point the cemiplimab hazard instantaneously drops to the underlying comparator curve (platinum-based chemotherapy or BSC depending on the analysis), following which cemiplimab is assumed to have the same hazard of death/progression or death as the underlying comparator curve.

Clinical expert feedback from an advisory board noted that the updated data supports the continued treatment benefit to [redacted]months.[5] Clinicians advised that as no data is available after [redacted] months, conservative estimates should be applied.

A.9 Key model assumptions and inputs

Analyses were conducted using the committee's preferred assumptions from the TA592 appraisal with the addition of the mature EMPOWER-CSCC 1 data to revisit survival analyses, continued treatment benefit assumptions, and updated utility and safety data. The updated overall survival analyses with the cost-effectiveness model for the platinum-based chemotherapy and BSC comparators are informed by the retrospective chart review and Sun 2019.

Table 15 presents the key changes in the model assumptions and inputs from NICE TA592 compared with the post-CDF submission.

Table 15: Key model assumptions and inputs

Model input and cross reference	Parameter/assumption		Source/Justification
	TA592	ID3883	
Overall survival extrapolation of cemiplimab (Section A.8.3.1)	Lognormal extrapolation (EMPOWER-CSCC 1, October 2017)	Lognormal extrapolation (EMPOWER-CSCC 1, July 2021, [redacted])	Further follow-up data from the pivotal trial (EMPOWER-CSCC 1) is incorporated into the model. Clinical expert validation from an advisory board in December 2021 indicated that the best fitting curve for the updated EMPOWER data was the lognormal distribution. This distribution had the best statistical fit
Progression-free survival extrapolation of cemiplimab (Section A.8.4.1)	Weibull extrapolation (EMPOWER-CSCC 1, October 2017)[a]	Second-order fractional polynomial (p0 p-1) extrapolation (EMPOWER-CSCC 1, July 2021, [redacted])	Data from the latest data cut from EMPOWER-CSCC 1 have been used for progression-free survival parametric extrapolation in the model. Goodness of fit statistics, visual inspection and clinical validation suggests that the second-order fractional polynomial (p0 p-1) is the best fitting extrapolation for the updated clinical data
Overall survival extrapolation for chemotherapy (Section A.8.3.2)	Gompertz; (Jarkowski, 2016)	Log-logistic (Retrospective chart review, ATT model 1)	Goodness of fit statistics, visual inspection and clinical validation suggests that the log-logistic curve is the best fitting extrapolation to the data
Overall survival extrapolation for BSC (Section A.8.3.3)	Gompertz, (Jarkowski, 2016)	Log-logistic (Sun 2019)	The log-logistic distribution was selected for the base case as this most closely reflected clinical opinion.
Progression free survival extrapolation for chemotherapy (Section A.8.4.2)	Weibull, (Jarkowski 2016)	No change	The chart review data were not considered reliable to inform PFS (Section A.6.2), therefore, there were no changes in the estimation of PFS for the chemotherapy arm from the original submission
Progression free survival for BSC (Section A.8.4.3)	Weibull, (Jarkowski 2016)	Patients assumed to start in post-progression health state	As the Sun 2019 paper did not report PFS data, all patients were conservatively assumed to start in the post-progression health state as there was insufficient evidence to inform PFS. This approach was considered reasonable by UK clinical experts
Continued treatment benefit	Cemiplimab hazard	Cemiplimab hazard	[redacted], showing

Model input and cross reference	Parameter/assumption		Source/Justification
	TA592	ID3883	
after stopping cemiplimab (Section A.8.5)	matches comparator hazard at 36 months	matches comparator hazard at 60 months	continuation of benefit. The analysis assumed benefit is maintained until 60 months after which cemiplimab is assumed to have the same hazard as the relevant comparator hazard. This assumption was supported by clinical expert feedback from the December 2021 advisory board
Key: a) Distribution changed to log-normal during NICE post-submission process			

A.10 Cost-effectiveness results (deterministic)

As discussed in Section A.6, the updated EMPOWER-CSCC 1 data has provided updated PFS, OS, quality of life and safety data. Further changes include the use of the retrospective chart review to inform comparative efficacy for standard of care with chemotherapy and the use of Sun 2019. to inform comparative efficacy for BSC.

The incremental cost-effectiveness ratio (ICER) for the updated company base case is £36,163 versus chemotherapy and £29,438 versus BSC using the PAS price for cemiplimab ([redacted]% PAS). The ICERs are [redacted] versus chemotherapy and [redacted] versus BSC using the cemiplimab list price, demonstrating that cemiplimab remains cost-effective using the July 2021 DCO for EMPOWER-CSCC 1.

The model assumes cemiplimab treatment effect continues to 60 months. Following this time point the cemiplimab hazard is conservatively assumed to equal that of the chosen comparator (chemotherapy or BSC). As chemotherapy and BSC are associated with different hazards following the 60-month cut point, benefits associated with cemiplimab will differ when comparing to chemotherapy or BSC.

Table 16: Cost-effectiveness results for cemiplimab versus chemotherapy (deterministic, PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (cemiplimab: log-normal for OS extrapolation, log-normal for PFS extrapolation, October 2017 EMPOWER-CSCC 1 data, *24-month stopping rule, ERG resource use costs, CDF entry MAA*, 36-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,693	£45,693
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence (*cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data,* 24-month stopping rule, ERG resource use costs, CDF exit MAA, *60-month hazard switching assumption*; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,093	£35,093
Cost-effectiveness analysis 3: New company base case (cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 60-month hazard switching assumption; chemotherapy: *log-logistic for OS extrapolation, chart review*)								

Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,163	£36,163
Key: CSCC, cutaneous squamous cell carcinoma; ERG, Evidence Review Group; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.								

Table 17: Cost-effectiveness results for cemiplimab versus BSC (deterministic, PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (cemiplimab: log-normal for OS extrapolation, October 2017 EMPOWER-CSCC 1 data, 24-month stopping rule, 36-month hazard switching assumption; BSC: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,463	£47,463
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence (*cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data,* 24-month stopping rule*, 60-month hazard switching assumption*; BSC: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,007	£38,007

Cost-effectiveness analysis 3: New company base case (cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, 60-month hazard switching assumption; BSC*log-logistic for OS extrapolation, Sun 2019*)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,438	£29,438
Key: CSCC, cutaneous squamous cell carcinoma; ERG, Evidence Review Group; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.								

A.11 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed for 1,000 iterations, in each iteration, the model inputs were randomly drawn from the specified distributions, summarized in Section A.15.12, Table 18.

The PSA scatter plots and cost-effectiveness acceptability curves for the analysis are presented in Figure 17 to Figure 20. The mean probabilistic incremental costs and QALYs gained from cemiplimab compared to chemotherapy and BSC are presented in Table 18 and Table 19. The deterministic and probabilistic outputs are similar, highlighting the robustness of the estimates.

Figure 17: Cost-effectiveness acceptability curve, **cemiplimab versus chemotherapy (PAS price) – B.3.8.1 (Figure 38, page 160)**

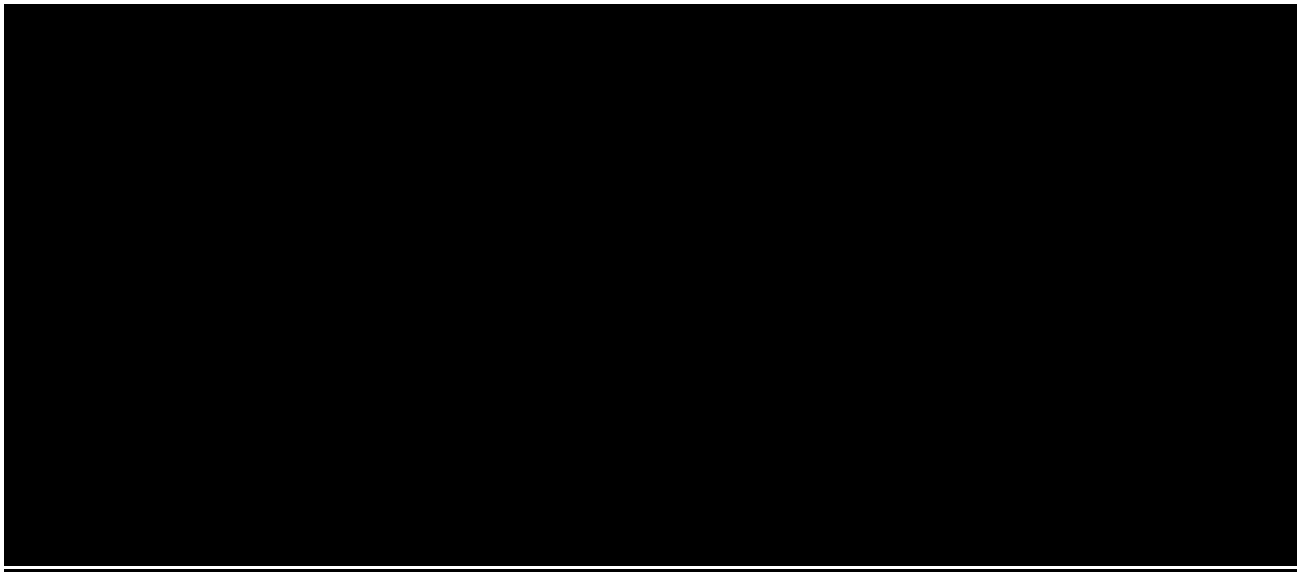


Figure 18: Cost-effectiveness acceptability curve, cemiplimab versus BSC (PAS price) – B.3.8.1 (Figure 42, page 163)

Figure 19: PSA scatterplot, cemiplimab versus chemotherapy (probabilistic, PAS price) – B.3.8.1 (Figure 37, page 159)

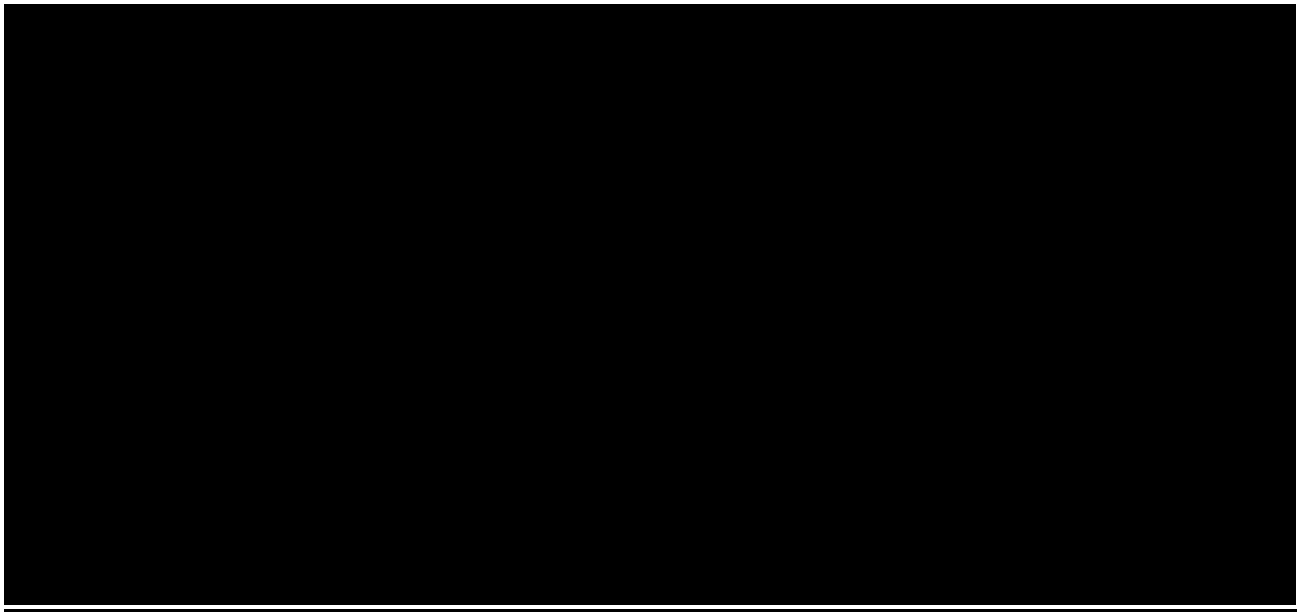


Figure 20: PSA scatterplot, cemiplimab versus best supportive care (probabilistic, PAS price) – B.3.8.1 (Figure 41, page 162)

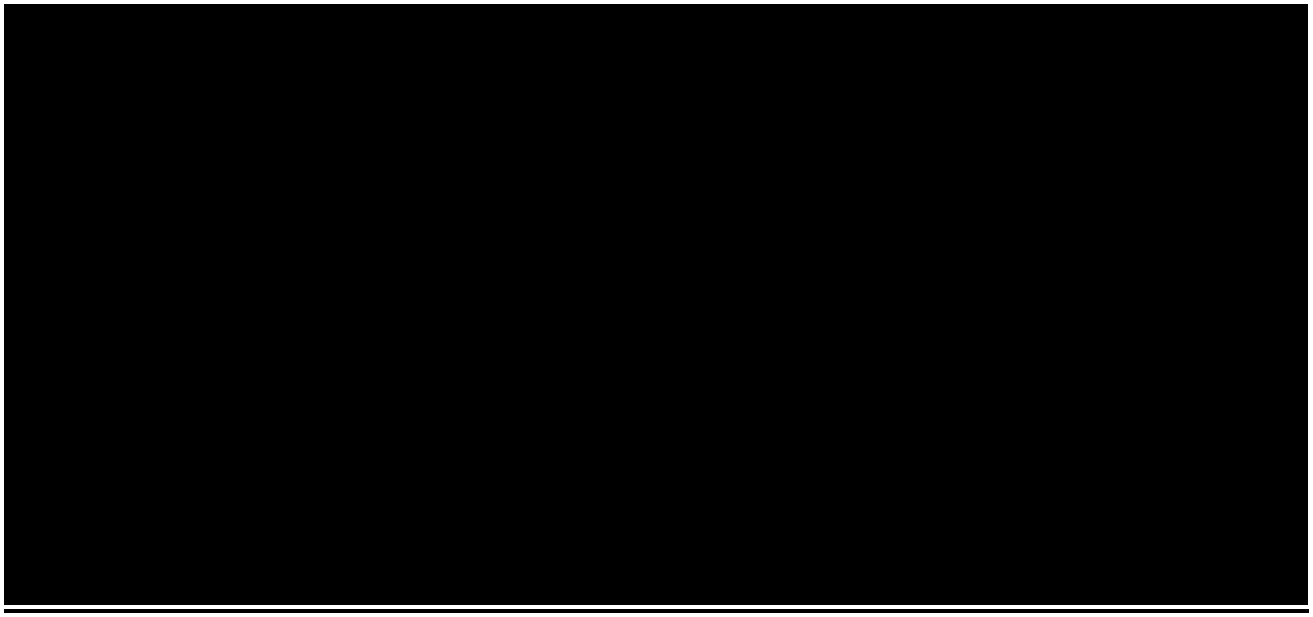


Table 18: Updated base case results for cemiplimab versus chemotherapy (probabilistic, PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental . costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	Incremental ICER (£/QALY)
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,995	£35,995
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 19: Updated base case results for cemiplimab versus BSC (probabilistic, PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental . costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	Incremental ICER (£/QALY)
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,211	£26,211
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

A.12 Key sensitivity and scenario analyses

Figure 21 and Figure 22 present the top 10 drivers of cost-effectiveness with descending sensitivity from the one-way sensitivity analysis at list prices. The ICERs were most sensitive to parameters relating to those informing OS and PFS estimates for cemiplimab and its comparators, utility and monthly health state costs. These are similar to those presented in the Company submission for TA592 (Appendix A.15.12), however, with greater follow-up, the uncertainty decreased around the impact on the ICER (range between the upper and lower bound is reduced).

Table **20** presents scenario analyses for each updated set of inputs in the cost-effectiveness model. Scenarios show that the data sources used for the comparison between cemiplimab and platinum-based chemotherapy/BSC are influential, but that results all remain within a similar cost-effective range.

Further scenarios investigate the impact of applying gradual treatment waning to cemiplimab estimates after the last datapoint of the trial at [redacted] months and no waning to investigate the impact of a sustained treatment effect expected with cemiplimab on cost-effectiveness outcomes.

Finally, a scenario investigates using the baseline characteristics of patients receiving cemiplimab in SACT to explore the impact of incorporating older patients into the cost-effectiveness modelling. This marginally increases the ICER estimates but cemiplimab remains cost-effective.

Taken together the analyses demonstrate that under the end of life criteria (see Section A.13) cemiplimab can be considered a cost-effective treatment for advanced CSCC with no ICER associated with parameters varied at their upper and lower bounds in OWSA exceeding £50,000/QALY, and probabilistic analyses suggesting that cemiplimab would be cost-effective in 100% of cases.

Figure 21 Tornado diagram showing OWSA results, cemiplimab versus chemotherapy (PAS price) – B.3.8.2 (Figure 44, page 164)

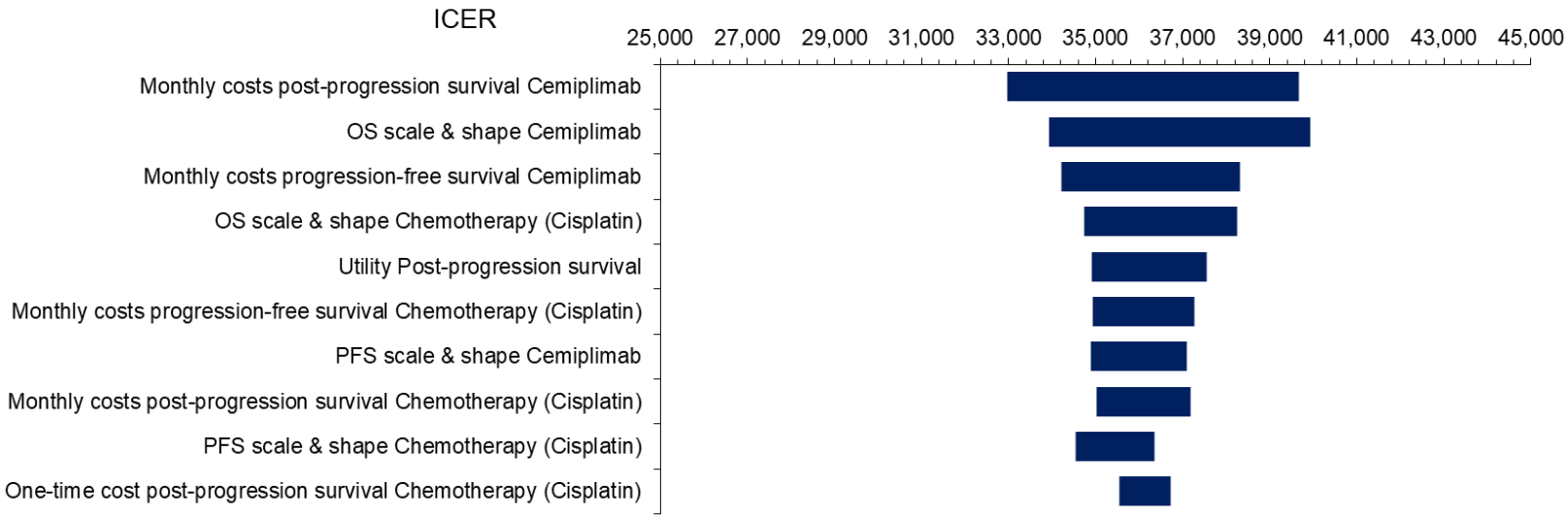


Figure 22 Tornado diagram showing OWSA results, cemiplimab versus BSC (list price) – B.3.8.2 (Figure 46, page 165)

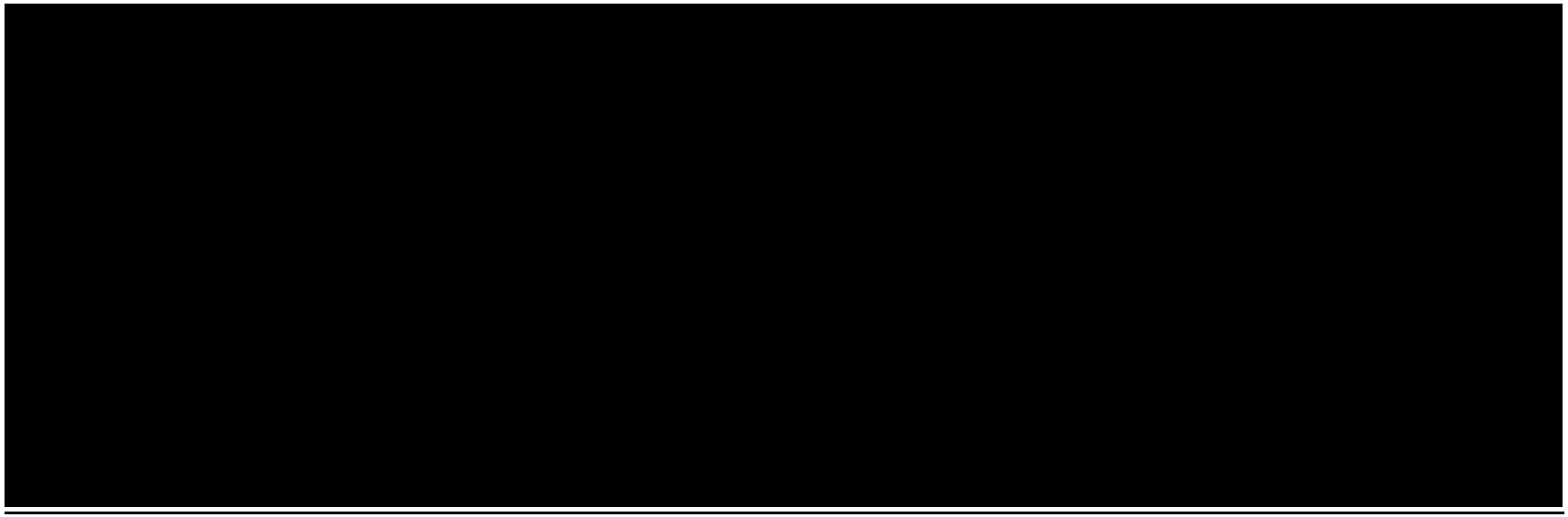


Table 20: Key scenario analyses (PAS price) – B.3.8.3 (Table 49, page 166)

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base case ICER vs.	
			Platinum-based chemotherapy	BSC
Base case			£36,163	£29,438
Survival for comparator arms informed by Jarkowski et al. 2016 *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with Jarkowski comparator data, OS Gompertz, PFS Weibull.*	Jarkowski survival data used for comparator OS	Alternative data source for comparator estimates	£36,446	£39,340
Use of ATC propensity score model 1 *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with ATC (cemiplimab), model 1 data, OS log-normal, PFS FP (p0, p-1).*	Analysis matching trial data to integrated chart review data	As trial data had more variability in ECOG and prior systemic therapy and a higher sample size, this model allows for inclusion of these prognostic factors. The ATC model 1 was used to match the best fitting ATT analysis used in the base case	£39,346	NA

Full ATT propensity score model *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with ATT (chart review), full model data, OS log-normal, PFS FP (p0, p-1).*	Propensity score model including ECOG status and Tumour location as prognostic factors	Insufficient overlap of variables, specifically, ECOG status, excluded these from the base case analyses. Full model explores impact of inclusion	£36,621	NA
SACT baseline characteristics *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with SACT baseline characteristics.*	SACT population age and gender data	Exploratory scenario to estimate cost-effectiveness results based on limited real-world data from NHS England clinical practice	£37,775	£30,953
No waning of treatment benefit (continuation of hazard trend) *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with continuation of hazard trend for cemiplimab.*	No loss of treatment effect	Exploratory scenario investigating no loss of treatment effect	£26,263	£24,663
Treatment waning applied between 60 and 96 months *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with gradual treatment waning*	Gradual loss of treatment effect between 60 and 96 months	Exploratory scenario investigating a gradual loss of treatment effect	£32,466	£26,002

between 60 and 96 months for cemiplimab.				

A.13 End-of-life criteria

It was highlighted within the MAA that meeting end-of-life was expected but was uncertain. The company believe that the available data and the opinion of the clinical community clearly demonstrates that cemiplimab meets the end-of-life criteria.

Table 21: End-of-life criteria – B.2.13 (Table 14, Page 84)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	All the available data suggest that without cemiplimab patients have a life expectancy less than 24 months. With respect to chemotherapy, median survival was estimated to be ~ 15 months by both the UK chart review and the Jarkowski 2016. Clinicians consulted also agreed that they would not expect patients receiving chemotherapy to survive beyond 2 years. With respect to BSC clinicians stated that they would not expect patients to survive longer than 6 months and median survival reported by Sun et al was 5 months.[5]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Cemiplimab offers a substantial extension to life for advanced CSCC patients. Median OS has still not been reached even with [redacted]months of data now available for EMPOWER. Survival is [redacted]% at[redacted] years. Given the survival associated with both chemotherapy and BSC, cemiplimab clearly offers a greater than 3-month extension to life for this patient population. This is supported by UK clinicians, who are seeing clinical practice align with the results of the EMPOWER-CSCC-1 trial with many patients having received the full two years of cemiplimab treatment. The SACT dataset despite the challenges highlighted in section A.6.5 also supports an extension to life of greater than 3 months.

A.14 Key issues and conclusions based on the data collected during the CDF review period

This submission attempts to address key issues identified during the appraisal of TA592. The data used to address these issues are summarised in Table 22 and described in more detail below. Following an economic evaluation addressing the key

issues, cemiplimab proves to be a clinically effective and cost-effective treatment option for advanced CSCC patients in the UK.

Table 22. Summary of key issues and conclusions

Issue noted by Committee	Data addressing uncertainty
Long-term treatment benefit of cemiplimab. In particular, the magnitude of any continued treatment benefit after a stopping rule	Updated 60-month data cut (July 2021) from EMPOWER-CSCC 1. Median OS is not yet reached, and survival rate being reported at [redacted] at [redacted] months. Survival extrapolations were also validated with clinicians, who advised on which models were most clinically plausible. The data at [redacted] months reflect that patients were subject to the 2-year stopping rule or progression, whichever came sooner.
Lack of reliable comparative evidence that is generalizable to UK clinical practice	The company conducted a retrospective chart review study of CSCC patients within a UK setting. The dataset provides comparative evidence generalizable to UK clinical practice and those reported by Jarkowski 2016. The OS data collected during this study informs the base case for this submission.
The baseline characteristics of patients included in the model	The baseline characteristics of patients receiving cemiplimab in UK clinical practice tend to be older and frailer than those patients included in the trial and the chart review study according to clinicians. Sanofi has presented a scenario using the baseline characteristics from the SACT database and results show cemiplimab to be cost-effective. Clinical experts at an advisory board in December 2021 noted that clinical practice has changed in recent years. Previously, only patients who were physiologically fit and more likely to be younger (< 75 years) could receive chemotherapy, others would receive BSC. But now patients who could not be prescribed chemotherapy are able to receive cemiplimab.

Key: CSCC, cutaneous squamous cell carcinoma; MAA, managed access agreement; RWE, real world evidence; SACT, systemic anti-cancer therapy

A.14.1 Long-term treatment benefit of cemiplimab. In particular, the magnitude of any continued treatment benefit after a stopping rule

The updated July 2021 DCO from EMPOWER-CSCC 1 supports the long-term benefit of treatment with cemiplimab. Revisiting these data has given more certainty to the survival extrapolations, with median OS not yet reached and survival rate being reported at [redacted] at [redacted]months maximum follow-up. Survival extrapolations were also validated with clinicians, who advised on which models were most clinically plausible. The latest DCO reflect that patients were subject to the 2-year stopping rule or progression, whichever came sooner. The data supports that a 2-year stopping rule would be suitable for cemiplimab in advanced CSCC and patients should expect to achieve long-term benefits beyond the 2 years. The company has also explored this continued treatment benefit within the model by maintaining benefit to [redacted]months as per the latest trial data; this assumption of continued benefit up to [redacted] months was supported by clinical experts.

A.14.2 Lack of reliable comparative evidence that is generalizable to UK clinical practice

A key area of uncertainty outlined within the MAA was the lack of reliable comparative evidence that is generalizable to the UK. The Company submission for TA592 used Jarkowski 2016 as the primary comparator dataset for CSCC patients receiving platinum-based chemotherapy. Despite limitations associated with a small sample size, differences in patient selection and a non-UK population, it was the most complete dataset available at the time and for PFS data remains the only source available.

There is still a limited amount of data for patients receiving BSC, as these patients are often treated in the community and have very poor outcomes. Clinicians believe these patients would greatly benefit from treatment with cemiplimab as they cannot tolerate chemotherapy. The company submitted a comparison to Sun 2019 at post submission stage. Sun 2019 as the only identified study assessing survival of patients who received BSC in the target population. Despite the limitations, such as small sample size, non-UK population, assumptions on patient characteristics for matching, and lack of PFS, Sun

2019 gave a rare opportunity to compare cemiplimab with BSC in the target population, and results from all three analysis methods showed cemiplimab to improve survival compared to BSC. Sun 2019 provides an important data source for BSC, as there are challenges associated with collecting data in the primary care setting where BSC patients are often treated, due to the lack of treatment options and nature of the disease.

Due to the limitations above of the comparator datasets available in this indication, specifically a non-UK population and small sample sizes, the company conducted a retrospective chart review study of CSCC patients within a UK setting. The dataset provides comparative evidence generalizable to UK clinical practice and the OS data collected during this study informs the base case for this submission. As is often the case with RWE studies, there were some limitations associated with the chart review and an audit was conducted to address these and ensure the population of the chart review was as close to the EMPOWER population as possible to provide a fair comparison. Another limitation was that PFS data were not reliable; therefore Jarkowski 2016 data on PFS had to be used. Compared to the initial submission, additional prognostic factors were available for matching from the chart review to the cemiplimab trials, but it should be noted the matching was done for OS only and the limited prognostic factors (due to limited patient characteristics reported by Jarkowski 2016) remain a consideration for PFS as per the initial submission (see Appendix A.16.1. Despite these limitations, the chart review is the only source of comparator data for the UK for CSCC patients. Additionally, the OS estimates from the chart review are comparable to the published estimates from Jarkowski 2016, and further demonstrate the poor survival outcomes expected with platinum-based chemotherapy compared to cemiplimab.

A.14.3 The baseline characteristics of patients included in the model

The baseline characteristics of patients included in the model are thought to be generalizable to the UK patient population based on baseline characteristics as demonstrated in the SACT dataset and the chart review study. The company has

reviewed global real world datasets, which show that similar baseline characteristics were shared between EMPOWER-CSCC 1 and patients in clinical practice.[12] However, there remains some differences, patients were generally a little older (between 74-83 years over 9 RWE studies) compared to 72 years within the cemiplimab trials. Some immunocompromised patients and those with higher ECOG status were excluded from the trial population but received cemiplimab in real life. Patients were much more heavily pre-treated with systemic therapies in the real world setting compared to the trial. However, when interpreting real world datasets the following should be taken into account, (i) the majority of real world studies have a shorter follow-up, (ii) they often lack consistent and/or central assessment of disease response and (iii) the patient population tend to be older and frailer (outlined above). We have previously noted in Section B.6 and B.7, that the OS data reported in SACT differs to the EMPOWER-CSCC 1 trial; the company consider this being the result of patients within SACT being frailer (higher ECOG status) and slightly older.

A.14.4 Unmet need

NICE TA592 noted that there was a high unmet need in this disease area and that patients have very few treatment options. This remains the case in 2021, with clinicians at an advisory board in December 2021 noting that there are many patients who are not eligible for systemic therapy or surgery that would be left with no treatment options and a prognosis of around 6 months to live. The availability of cemiplimab through the CDF has transformed the treatment of advanced CSCC with cemiplimab largely displacing the use of chemotherapy, providing a treatment options for patients otherwise resigned to palliative care through BSC and, owing to its efficacy and good tolerability it has become the treatment of choice for patients for whom there is no other treatment option available and prior to the introduction of cemiplimab had a median survival of 5 months[3, 5].

In addition to being associated with poor survival outcomes advanced CSCC is a disabling and disfiguring disease. Further information and images of patients are summarized in Section B.1.3 (page 14) of NICE TA592. Locally advanced lesions and

tumours can cause disfigurement of the patients. Lesions often appear in places exposed to the sun such as the face and neck, and often lesions are unresectable due to their proximity to the eyes, mouth and nose and so would lead to impairment. Perineural invasion (where the tumour spreads into the space surrounding a nerve) is often clinically occult (concealed) but can result in pain, itching, numbness and tingling and is associated with poor outcomes for CSCC.[13, 14] Patients with disfigurement due to cancer and its treatments have been shown to have a reduced HRQoL, affecting physical and psychological health and social relationships. [15]

Conclusion

Cemiplimab meets NICE's end of life criteria and provides a cost-effective treatment option for advanced CSCC patients, addressing a particularly high unmet need. The updated trial data from EMPOWER-CSCC 1 addresses the committees concerns regarding continued treatment benefit following the two-year stopping rule. The chart review data provides comparative evidence that is generalizable to a UK population whilst Sun 2019 provides more appropriate comparator data for BSC. The chart review and the SACT dataset support the conclusion that the EMPOWER-CSCC 1 trial population has generally comparable baseline characteristics to the UK population, despite highlighting that frailer and sicker patients who historically would have received BSC would now be treated with cemiplimab in clinical practice. Clinicians support that cemiplimab has provided a step change within the treatment landscape for patients with advanced CSCC during its time available on the CDF. The conservative and comprehensive approach to the updated analyses should reassure the committee that cemiplimab can

A.15 Appendices

A.15.1 Summary of patient baseline characteristics – Empower-CSCC 1, Study 1423, SACT cohort, Jarkowski, Sun, retrospective Chart review (UK cohort)

Table 23. Summary of baseline patient characteristics for main data sources within this submission

		Cemiplimab				**BSC**	**Chemotherapy**	
		EMPOWER-CSCC-1	Study 1423	Pooled Study 1423 & EMPOWER	**SACT database (CDF)**	**Sun et al, 2019**	[redacted]	**Jarkowksi et al, 2016**
N		193	26	219	352	32	[redacted]	26
Disease severity	laCSCC	78 (40.4)	10 (38.5)	88 (40.2)	172 (49)	12 (42.9)	[redacted]	19 (76)
	mCSCC	115 (59.6)	16 (61.5)	131 (59.8)	180 (51)	16 (57.1)	[redacted]	6 (24)
Age median (range)		72 (38-96)	72.5 (52-88)	72 (38-96)	77	73 (43-89)	[redacted]	66.4
Gender n (%)	Male	161 (83.4)	21 (80.8)	182 (83.1)	262 (74)	26 (81.3)	[redacted]	18 (72
Differentiation n (%)	Well	[redacted]	2 (7.7)	[redacted]	-	-	[redacted]	-
	Undifferentiated	[redacted]	17 (65.4)	[redacted]	-		[redacted]	
	Undetermined	[redacted]	7 (26.9)	[redacted]	-		[redacted]	
Tumour location n (%)	Head and neck	[redacted]	19 (73.1)	[redacted]	-	32 (100)	[redacted]	11(44.0)
	Trunk	[redacted]	2 (7.7)	[redacted]	-	0 (0)	[redacted]	7 (28.0)
	Extremities	[redacted]	5 (19.2)	[redacted]	-	0 (0)	[redacted]	3 (12.0)

T stage n (%)	T0 Tis Tx T1 T2 T3 T4	[redacted]	- - 8 (30.8) 3 (11.5) 10 (38.5) 2 (7.7) 3 (11.5)	[redacted]	- - - - - - -		[redacted]	- - - - - - -
ECOG performance status n (%)	0 1 2	86 (44.6) 107 (55.4) -	10 (38.5) 16 (61.5) -	96 (43.8) 123 (56.2)	64 (18) 223 (63) 14 (4) 51 missing		[redacted]	- - -
Prior systemic therapy n (%)		65 (33.7)	15 (57.7)	80 (36.5)	-	-	[redacted]	8 (32)
Prior radiation n (%)		[redacted]	21 (80.8)	[redacted]	-		[redacted]	-

A.15.2 OS proportional hazards, extrapolations and hazard plots

Proportional hazards

Figure 23: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423) versus integrated chart review UK integrated analysis cohort, overall survival

Abbreviations: PBC, platinum-based chemotherapy.

Figure 24: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423) versus integrated Jarkowski et al. (2016), overall survival

Figure 25: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423) versus integrated Sun et al. (2019), overall survival

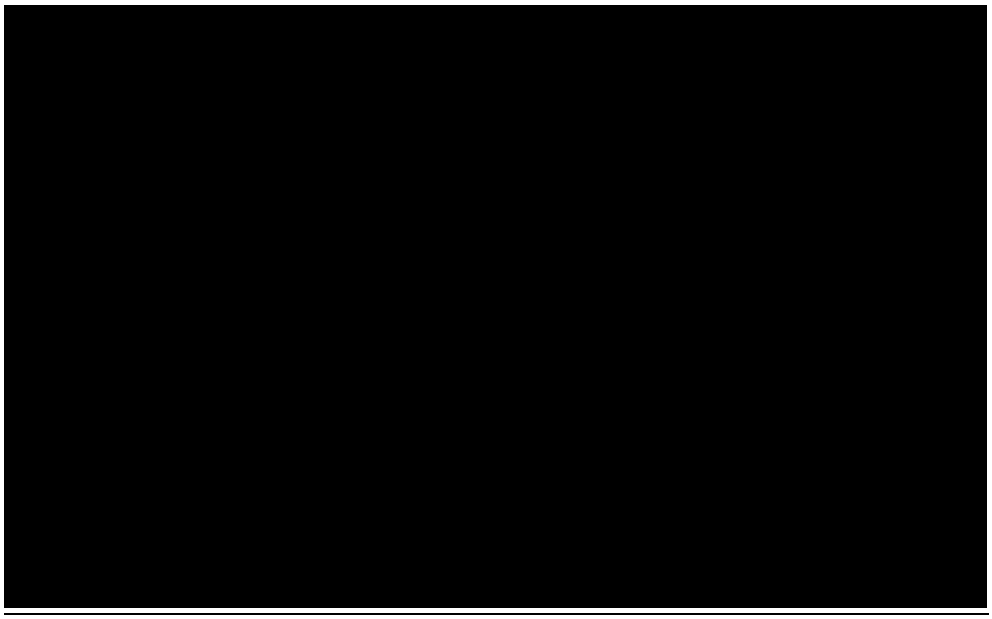


Figure 26: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423) versus integrated chart review UK integrated analysis cohort (ATT full model trimmed), overall survival

Abbreviations: ATT, average treatment effect on treated; PBC, platinum-based chemotherapy; UK, United Kingdom.

Figure 27: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423) versus integrated chart review UK integrated analysis cohort (ATT model 1 trimmed), overall survival

Abbreviations: ATT, average treatment effect on treated; PBC, platinum-based chemotherapy; UK, United Kingdom.

Figure 28: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423) versus integrated chart review UK integrated analysis cohort (ATT model 2 trimmed), overall survival

Abbreviations: ATT, average treatment effect on treated; UK, PBC, platinum-based chemotherapy; United Kingdom.

Figure 29: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423, ATC full model trimmed) versus integrated chart review UK integrated analysis cohort, overall survival

Abbreviations: ATC, average treatment effect on control; PBC, platinum-based chemotherapy; UK, United Kingdom.

Figure 30: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423, ATC model 1 trimmed) versus integrated chart review UK integrated analysis cohort, overall survival

Abbreviations: ATC, average treatment effect on control; PBC, platinum-based chemotherapy; UK, United Kingdom.

Figure 31: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423, ATC model 2 trimmed) versus integrated chart review UK integrated analysis cohort, overall survival

Abbreviations: ATC, average treatment effect on control; UK, PBC, platinum-based chemotherapy; United Kingdom.

Survival extrapolations

Figure 32: Extrapolated overall survival for cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423), Kaplan Meier

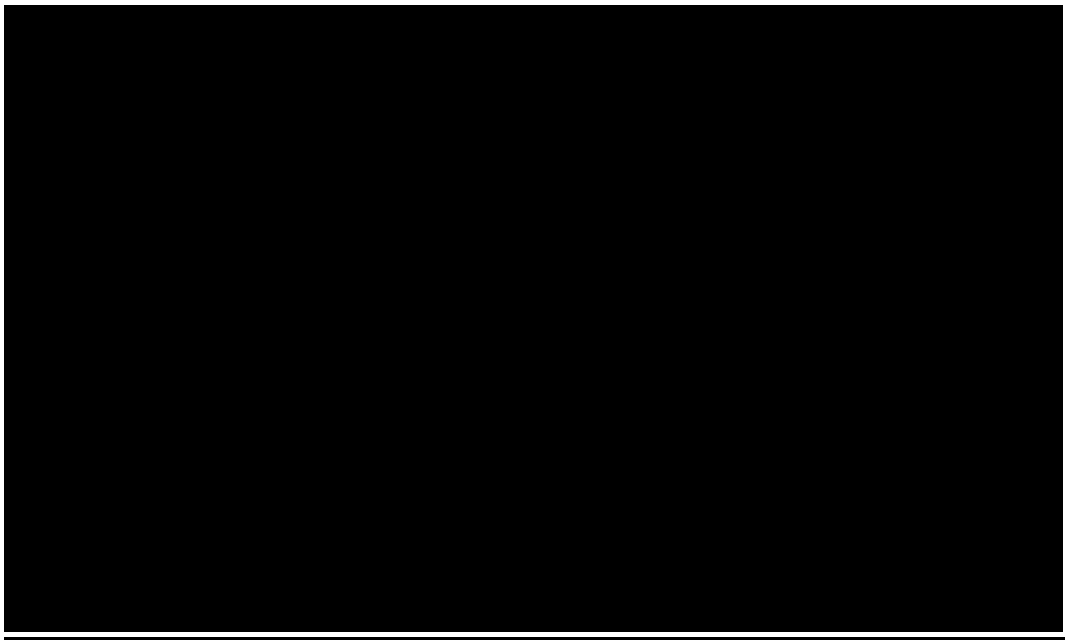


Figure 33: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on naïve analysis (EMPOWER-CSCC 1 only)

Figure 34: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on naïve analysis (chart review UK integrated cohort)

Abbreviations: UK, United Kingdom.

Figure 35: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on naïve analysis (Jarkowski et al. 2016)

Figure 36: Extrapolated overall survival for best supportive care estimated using alternative parametric models based on naïve analysis (Sun et al. 2019)

Figure 37: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on ATT adjusted analysis; model 1, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort)

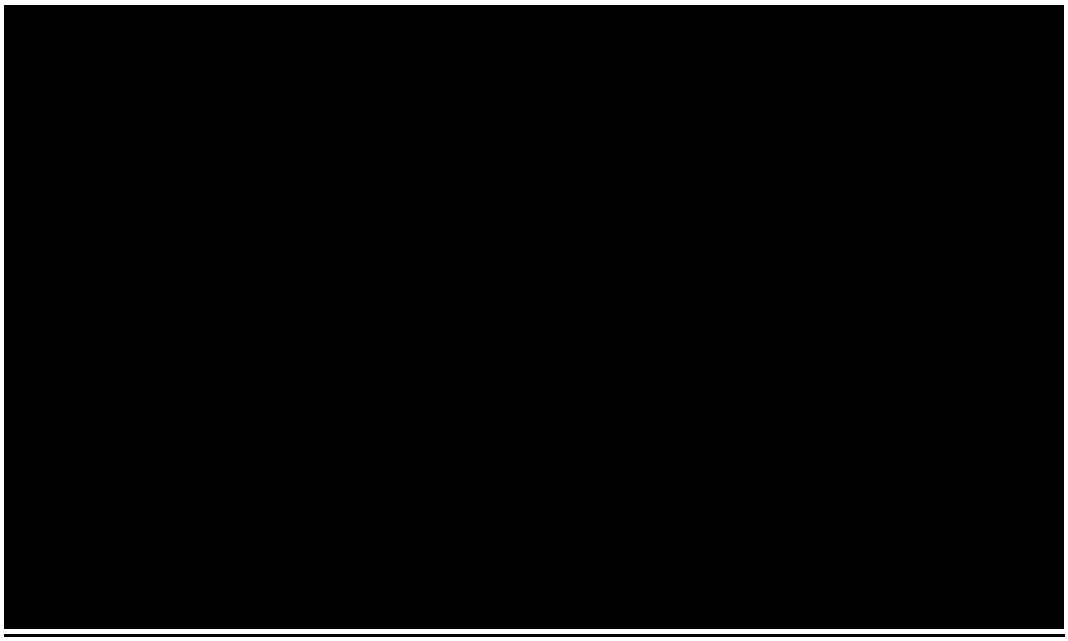


Figure 38: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on ATT adjusted analysis; full model, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort)

Abbreviations: ATT, average treatment effect on treated; UK, United Kingdom.

Figure 39: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on ATT adjusted analysis; model 2, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort)

Abbreviations: ATT, average treatment effect on treated; UK, United Kingdom.

Figure 40: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on ATC adjusted analysis; full model,

trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort)

Abbreviations: ATC, average treatment effect on control; UK, United Kingdom.

Figure 41: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on ATC adjusted analysis; model 1, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort)

Abbreviations: ATC, average treatment effect on control; UK, United Kingdom.

Figure 42: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on ATC adjusted analysis; model 2, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort)

Abbreviations: ATC, average treatment effect on control; UK, United Kingdom.

Figure 43: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on STC adjusted analysis (pooled EMPOWER-CSCC 1/Study 1423 and Jarkowski et al. 2016)

Abbreviations: STC, simulated treatment comparison.

Figure 44: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on STC adjusted analysis (pooled EMPOWER-CSCC 1/Study 1423 and Sun et al. 2019)

Abbreviations: STC, simulated treatment comparison.

Hazard plots

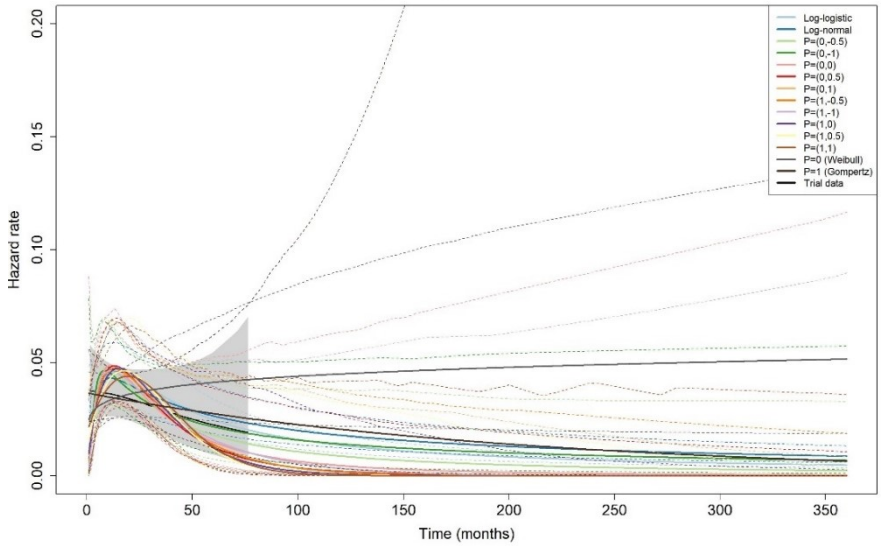
Figure 45: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on naïve analysis (pooled EMPOWER-CSCC 1 and Study 1423), hazards over time

Notes: Grey = observed data period.

Figure 46: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on naïve analysis (EMPOWER-CSCC 1 only), hazards over time

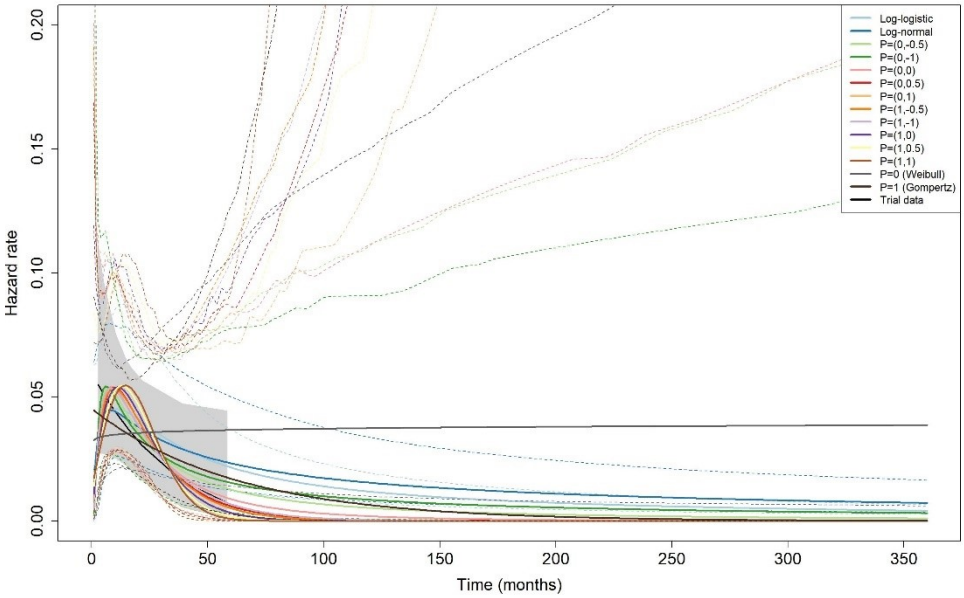
Notes: Grey = observed data period.

Figure 47: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on naïve analysis (chart review UK integrated cohort), hazards over time



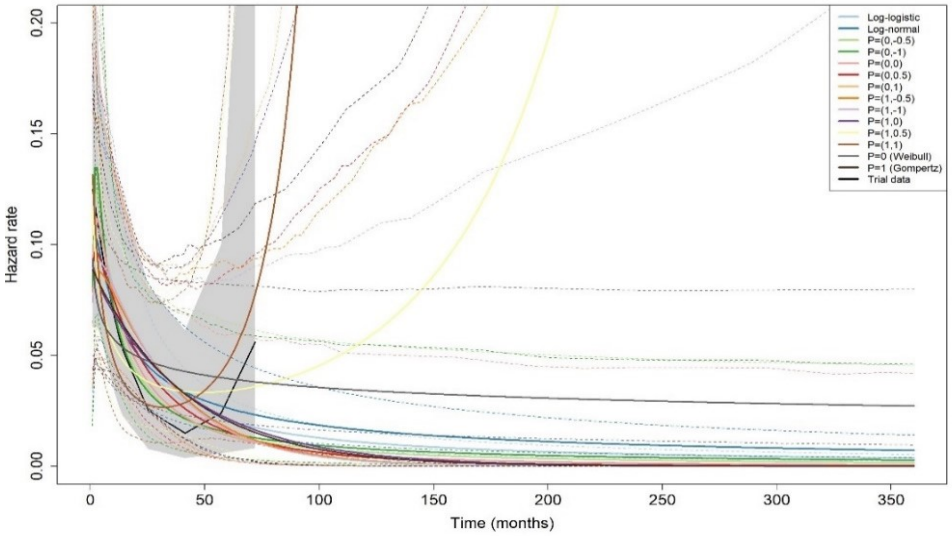
Notes: Grey = observed data period. **Abbreviations:** UK, United Kingdom.

Figure 48: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on naïve analysis (Jarkowski et al. 2016), hazards over time



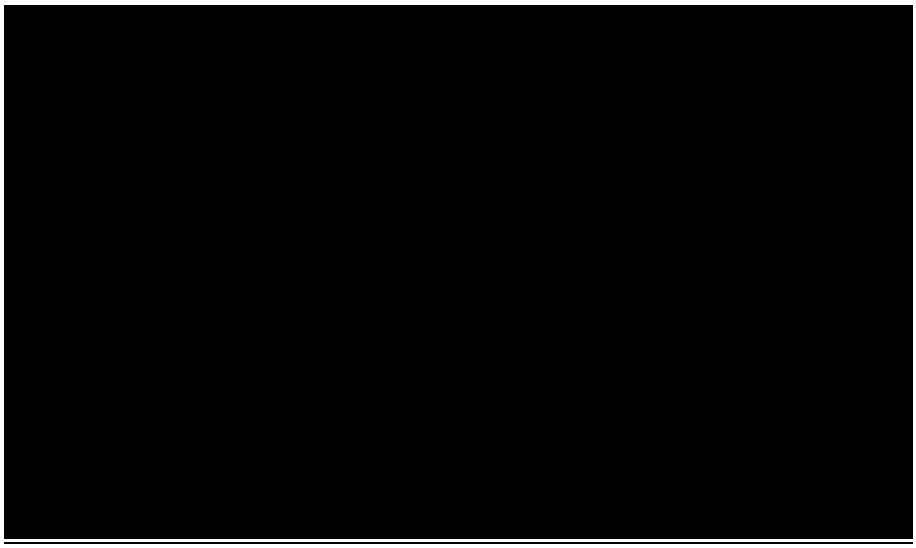
Notes: Grey = observed data period.

Figure 49: Extrapolated overall survival for best supportive care estimated using alternative parametric models based on naïve analysis (Sun et al. 2019), hazards over time



Notes: Grey = observed data period.

Figure 50: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on ATT adjusted analysis; full model, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort), hazards over time



Notes: Grey = observed data period. **Abbreviations:** ATT, average treatment effect on treated; UK, United Kingdom.

Figure 51: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on ATT adjusted analysis; model 1, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort), hazards over time

Notes: Grey = observed data period. **Abbreviations:** ATT, average treatment effect on treated; UK, United Kingdom.

Figure 52: Extrapolated overall survival for platinum-based chemotherapy estimated using alternative parametric models based on ATT adjusted analysis; model 2, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort), hazards over time

Notes: Grey = observed data period. **Abbreviations:** ATT, average treatment effect on treated; UK, United Kingdom.

Figure 53: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on ATC adjusted analysis; full model, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort), hazards over time

Notes: Grey = observed data period. **Abbreviations:** ATC, average treatment effect on control; UK, United Kingdom.

Figure 54: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on ATC adjusted analysis; model 1, trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort), hazards over time

Notes: Grey = observed data period. **Abbreviations:** ATC, average treatment effect on control; UK, United Kingdom.

Figure 55: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on ATC adjusted analysis; model 2,

trimmed (pooled EMPOWER-CSCC 1/Study 1423 and chart review UK integrated cohort), hazards over time

Notes: Grey = observed data period. **Abbreviations:** ATC, average treatment effect on control; UK, United Kingdom.

Figure 56: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on STC adjusted analysis (pooled EMPOWER-CSCC 1/Study 1423 and Jarkowski et al. 2016), hazards over time

Notes: Grey = observed data period. **Abbreviations:** STC, simulated treatment comparison.

Figure 57: Extrapolated overall survival for cemiplimab estimated using alternative parametric models based on STC adjusted analysis (pooled EMPOWER-CSCC 1/Study 1423 and Sun et al. 2019), hazards over time

Notes: Grey = observed data period. **Abbreviations:** STC, simulated treatment comparison.

A.15.3 PFS extrapolations and hazard plots

Proportional hazards

Figure 58: Log-log plots, cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423) versus integrated Jarkowski et al. (2016), progression-free survival

Survival extrapolations

Figure 59: Progression-free survival for cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423), Kaplan Meier

Figure 60: Extrapolated progression-free survival for cemiplimab estimated using alternative parametric models based on naïve analysis (EMPOWER-CSCC 1 only)

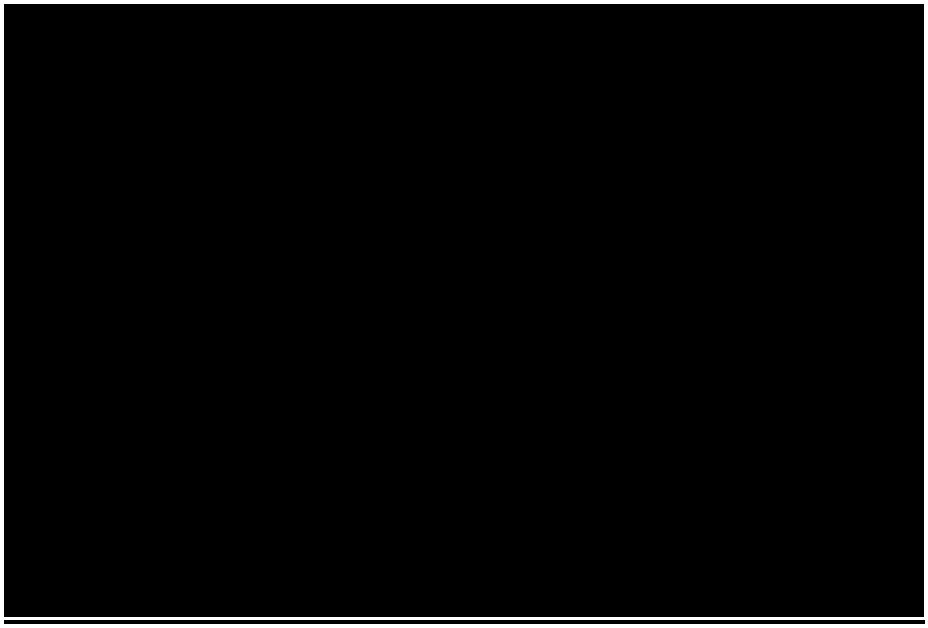
Figure 61: Extrapolated progression-free survival for platinum-based chemotherapy estimated using alternative parametric models based on naïve analysis (Jarkowski et al. 2016)

Figure 62: Extrapolated progression-free survival for cemiplimab estimated using alternative parametric models based on STC adjusted analysis (pooled EMPOWER-CSCC 1/Study 1423 and Jarkowski et al. 2016)

Abbreviations: STC, simulated treatment comparison.

Hazard plots

Figure 63: Extrapolated progression-free survival for cemiplimab estimated using alternative parametric models based on naïve analysis (pooled EMPOWER-CSCC 1 and Study 1423), hazards over time



Notes: Grey = observed data period.

Figure 64: Extrapolated progression-free survival for cemiplimab estimated using alternative parametric models based on naïve analysis (EMPOWER-CSCC 1 only), hazards over time

Notes: Grey = observed data period.

Figure 65: Extrapolated progression-free survival for platinum-based chemotherapy estimated using alternative parametric models based on naïve analysis (Jarkowski et al. 2016), hazards over time

Notes: Grey = observed data period.

Figure 66: Extrapolated progression-free survival for cemiplimab estimated using alternative parametric models based on STC adjusted analysis (pooled EMPOWER-CSCC 1/Study 1423 and Jarkowski et al. 2016), hazards over time

Notes: Grey = observed data period. **Abbreviations:** STC, simulated treatment comparison.

A.15.4 Survival goodness of fit statistics

Table 24: Goodness of fit statistics of alternative parametric models for progression-free and overall survival

Parametric distribution	PFS		OS	
	AIC	BIC	AIC	BIC
Naïve cemiplimab using EMPOWER-CSCC 1 only				
Weibull (p0)	909.67	916.20	736.07	742.59
Second-order FP (p0 p-1)	872.05	881.84	732.01	741.80
Second-order FP (p0 p-0.5)	877.93	887.72	732.80	742.59
Second-order FP (p0 p0)	886.15	895.94	733.97	743.75
Second-order FP (p0 p0.5)	895.75	905.54	735.32	745.11
Second-order FP (p0 p1)	903.74	913.53	736.39	746.18
Gompertz (p1)	902.18	908.71	734.47	741.00
Second-order FP (p1 p-1)	899.44	909.23	735.50	745.29
Second-order FP (p1 p-0.5)	902.82	912.61	736.23	746.02

Second-order FP (p1 p0)	903.74	913.53	736.39	746.18
Second-order FP (p1 p0.5)	897.69	907.47	735.67	745.46
Second-order FP (p1 p1)	889.87	899.65	734.90	744.69
Log-normal	890.38	896.90	731.83	738.35
Log-logistic	899.94	906.47	734.61	741.14
Pooled EMPOWER-CSCC 1 and Study 1423				
Weibull (P1=0)	1011.19	1017.97	828.34	835.12
Second-order FP P1=0, P2=-1	975.35	985.52	823.16	833.32
Second-order FP P1=0, P2=-0.5	981.27	991.44	824.06	834.23
Second-order FP P1=0, P2=0	989.64	999.81	923.11	933.28
Second-order FP P1=0, P2=0.5	999.29	1009.46	826.75	836.92
Second-order FP P1=0, P2=1	1006.82	1016.99	827.96	838.12
P1=1 (Gompertz)	1005.79	1012.56	825.98	832.75
Second-order FP P1=1, P2=-1	1003.59	1013.76	826.76	836.92
Second-order FP P1=1, P2=-0.5	1006.85	1017.02	827.59	837.76
Second-order FP P1=1, P2=0	1006.82	1016.99	827.96	838.12
Second-order FP P1=1, P2=0.5	999.39	1009.56	827.42	837.59
Second-order FP P1=1, P2=1	991.26	1001.42	826.80	836.97
Log-normal	991.61	998.39	823.28	830.05
Log-logistic	1001.89	1008.67	826.50	833.28
Naïve platinum-based chemotherapy using chart review UK integrated cohort				
Weibull (p0)	--	--	389.56	393.75
Second-order FP (p0 p-1)	--	--	383.66	389.94
Second-order FP (p0 p-0.5)	--	--	382.75	389.04
Second-order FP (p0 p0)	--	--	382.50	388.79
Second-order FP (p0 p0.5)	--	--	383.14	389.43
Second-order FP (p0 p1)	--	--	384.52	390.80
Gompertz (p1)	--	--	390.21	394.40
Second-order FP (p1 p-1)	--	--	383.33	389.61
Second-order FP (p1 p-0.5)	--	--	383.40	389.68
Second-order FP (p1 p0)	--	--	384.52	390.80
Second-order FP (p1 p0.5)	--	--	386.61	392.90
Second-order FP (p1 p1)	--	--	388.83	395.11
Log-normal	--	--	381.67	385.86
Log-logistic	--	--	382.13	386.32
Naïve platinum-based chemotherapy using Jarkowski et al. 2016				
Weibull (p0)	120.04	121.82	125.92	127.70
Second-order FP (p0 p-1)	118.71	121.38	124.78	127.45
Second-order FP (p0 p-0.5)	118.74	121.41	124.73	127.40
Second-order FP (p0 p0)	118.74	121.41	124.63	127.30
Second-order FP (p0 p0.5)	118.71	121.38	124.47	127.14
Second-order FP (p0 p1)	118.65	121.32	124.32	126.99
Gompertz (p1)	117.79	119.57	125.29	127.07

Second-order FP (p1 p-1)	118.24	120.91	124.28	126.96
Second-order FP (p1 p-0.5)	118.44	121.11	124.31	126.98
Second-order FP (p1 p0)	118.65	121.32	124.32	126.99
Second-order FP (p1 p0.5)	118.79	121.46	124.35	127.02
Second-order FP (p1 p1)	118.79	121.46	124.40	127.07
Log-normal	117.28	119.06	123.41	125.19
Log-logistic	117.59	119.38	123.68	125.46
Naïve best supportive care using Sun et al. 2019				
Weibull (p0)	--	--	131.57	133.56
Second-order FP (p0 p-1)	--	--	127.09	130.08
Second-order FP (p0 p-0.5)	--	--	128.04	131.03
Second-order FP (p0 p0)	--	--	129.53	132.51
Second-order FP (p0 p0.5)	--	--	131.34	134.33
Second-order FP (p0 p1)	--	--	132.79	135.78
Gompertz (p1)	--	--	130.81	132.80
Second-order FP (p1 p-1)	--	--	131.59	134.58
Second-order FP (p1 p-0.5)	--	--	132.36	135.34
Second-order FP (p1 p0)	--	--	132.79	135.78
Second-order FP (p1 p0.5)	--	--	131.69	134.68
Second-order FP (p1 p1)	--	--	129.76	132.74
Log-normal	--	--	127.21	129.21
Log-logistic	--	--	128.12	130.12
ATT adjusted platinum-based chart review UK integrated cohort (Model 1, trimmed)				
Model	--	--	1020.21	1024.40
Second-order FP (p0 p-1)	--	--	995.11	1001.40
Weibull (P1=0)	--	--	990.56	996.84
Second-order FP P1=0, P2=-1	--	--	987.53	993.81
Second-order FP P1=0, P2=-0.5	--	--	986.49	992.77
Second-order FP P1=0, P2=0	--	--	988.09	994.38
Second-order FP P1=0, P2=0.5	--	--	1014.53	1018.72
Second-order FP P1=0, P2=1	--	--	989.01	995.29
P1=1 (Gompertz)	--	--	987.30	993.58
Second-order FP P1=1, P2=-1	--	--	988.09	994.38
Second-order FP P1=1, P2=-0.5	--	--	991.81	998.09
Second-order FP P1=1, P2=0	--	--	996.91	1003.19
Second-order FP P1=1, P2=0.5	--	--	995.32	999.51
Second-order FP P1=1, P2=1	--	--	996.30	1000.49
ATT adjusted platinum-based chemotherapy using pooled EMPOWER-CSCC 1/Study 1623 and chart review UK integrated cohort (full model, trimmed)				
Weibull (p0)	--	--	865.12	869.31
Second-order FP (p0 p-1)	--	--	809.32	815.60
Second-order FP (p0 p-0.5)	--	--	805.04	811.33
Second-order FP (p0 p0)	--	--	803.87	810.15

Second-order FP (p0 p0.5)	--	--	805.96	812.25
Second-order FP (p0 p1)	--	--	810.70	816.99
Gompertz (p1)	--	--	841.54	845.73
Second-order FP (p1 p-1)	--	--	806.64	812.92
Second-order FP (p1 p-0.5)	--	--	807.23	813.51
Second-order FP (p1 p0)	--	--	810.70	816.99
Second-order FP (p1 p0.5)	--	--	816.85	823.13
Second-order FP (p1 p1)	--	--	823.84	830.12
Log-normal	--	--	835.06	839.24
Log-logistic	--	--	839.63	843.82
ATT adjusted platinum-based chemotherapy using pooled EMPOWER-CSCC 1/Study 1623 and chart review UK integrated cohort (model 2, trimmed)				
Weibull (p0)	--	--	1013.79	1017.98
Second-order FP (p0 p-1)	--	--	990.71	996.99
Second-order FP (p0 p-0.5)	--	--	986.44	992.72
Second-order FP (p0 p0)	--	--	983.27	989.55
Second-order FP (p0 p0.5)	--	--	982.14	988.42
Second-order FP (p0 p1)	--	--	987.80	994.08
Gompertz (p1)	--	--	1008.00	1012.19
Second-order FP (p1 p-1)	--	--	984.54	990.82
Second-order FP (p1 p-0.5)	--	--	982.82	989.10
Second-order FP (p1 p0)	--	--	983.36	989.64
Second-order FP (p1 p0.5)	--	--	987.25	993.54
Second-order FP (p1 p1)	--	--	991.21	997.49
Log-normal	--	--	990.21	994.40
Log-logistic	--	--	991.22	995.41
ATC adjusted cemiplimab using pooled EMPOWER-CSCC 1/Study 1623 and chart review UK integrated cohort (full model, trimmed)				
Weibull (p0)	--	--	160.97	167.75
Second-order FP (p0 p-1)	--	--	161.24	171.41
Second-order FP (p0 p-0.5)	--	--	161.40	171.56
Second-order FP (p0 p0)	--	--	161.62	171.79
Second-order FP (p0 p0.5)	--	--	161.94	172.11
Second-order FP (p0 p1)	--	--	162.28	172.45
Gompertz (p1)	--	--	160.55	167.32
Second-order FP (p1 p-1)	--	--	161.70	171.87
Second-order FP (p1 p-0.5)	--	--	161.96	172.12
Second-order FP (p1 p0)	--	--	162.28	172.45
Second-order FP (p1 p0.5)	--	--	162.50	172.67
Second-order FP (p1 p1)	--	--	162.54	172.71
Log-normal	--	--	159.67	166.44
Log-logistic	--	--	160.43	167.21

ATC adjusted cemiplimab using pooled EMPOWER-CSCC 1/Study 1623 and chart review UK integrated cohort (model 1, trimmed)				
Weibull (p0)	--	--	206.84	213.62
Second-order FP (p0 p-1)	--	--	207.52	217.69
Second-order FP (p0 p-0.5)	--	--	207.76	217.93
Second-order FP (p0 p0)	--	--	208.09	218.25
Second-order FP (p0 p0.5)	--	--	208.44	218.61
Second-order FP (p0 p1)	--	--	208.72	218.88
Gompertz (p1)	--	--	206.76	213.54
Second-order FP (p1 p-1)	--	--	208.12	218.29
Second-order FP (p1 p-0.5)	--	--	208.42	218.59
Second-order FP (p1 p0)	--	--	208.72	218.88
Second-order FP (p1 p0.5)	--	--	208.71	218.88
Second-order FP (p1 p1)	--	--	208.40	218.57
Log-normal	--	--	205.94	212.72
Log-logistic	--	--	206.58	213.36
ATC adjusted cemiplimab using pooled EMPOWER-CSCC 1/Study 1623 and chart review UK integrated cohort (model 2, trimmed)				
Weibull (p0)	--	--	256.62	263.40
Second-order FP (p0 p-1)	--	--	257.50	267.67
Second-order FP (p0 p-0.5)	--	--	257.93	268.10
Second-order FP (p0 p0)	--	--	258.39	268.55
Second-order FP (p0 p0.5)	--	--	258.61	268.78
Second-order FP (p0 p1)	--	--	258.48	268.65
Gompertz (p1)	--	--	256.75	263.53
Second-order FP (p1 p-1)	--	--	258.46	268.62
Second-order FP (p1 p-0.5)	--	--	258.72	268.89
Second-order FP (p1 p0)	--	--	258.48	268.65
Second-order FP (p1 p0.5)	--	--	257.49	267.66
Second-order FP (p1 p1)	--	--	256.46	266.63
Log-normal	--	--	256.57	263.35
Log-logistic	--	--	257.03	263.81
STC adjusted cemiplimab using pooled EMPOWER-CSCC 1/Study 1623 and Jarkowski et al. 2016				
Weibull (p0)	1695.38	1702.15	1099.46	1106.24
Second-order FP (p0 p-1)	1686.56	1696.73	1098.65	1108.82
Second-order FP (p0 p-0.5)	1692.36	1702.52	1099.70	1109.87
Second-order FP (p0 p0)	1697.14	1707.30	1100.91	1111.07
Second-order FP (p0 p0.5)	1693.09	1703.26	1101.43	1111.59
Second-order FP (p0 p1)	1680.35	1690.52	1101.13	1111.30
Gompertz (p1)	1704.34	1711.12	1100.92	1107.70
Second-order FP (p1 p-1)	1705.91	1716.08	1102.52	1112.68
Second-order FP (p1 p-0.5)	1705.10	1715.27	1102.89	1113.06

Second-order FP (p1 p0)	1680.35	1690.52	1101.13	1111.30
Second-order FP (p1 p0.5)	1641.45	1651.61	1098.01	1108.18
Second-order FP (p1 p1)	1617.29	1627.46	1095.68	1105.85
Log-normal	1701.75	1708.53	1100.21	1106.99
Log-logistic	1718.67	1725.45	1100.46	1107.24
STC adjusted cemiplimab using pooled EMPOWER-CSCC 1/Study 1423 and Sun et al. 2019				
Weibull (p0)	--	--	1189.79	1196.57
Second-order FP (p0 p-1)	--	--	1188.57	1198.74
Second-order FP (p0 p-0.5)	--	--	1189.73	1199.90
Second-order FP (p0 p0)	--	--	1191.06	1201.23
Second-order FP (p0 p0.5)	--	--	1191.73	1201.90
Second-order FP (p0 p1)	--	--	1191.58	1201.75
Gompertz (p1)	--	--	1191.08	1197.86
Second-order FP (p1 p-1)	--	--	1192.54	1202.71
Second-order FP (p1 p-0.5)	--	--	1193.08	1203.25
Second-order FP (p1 p0)	--	--	1191.58	1201.75
Second-order FP (p1 p0.5)	--	--	1188.70	1198.87
Second-order FP (p1 p1)	--	--	1186.51	1196.68
Log-normal	--	--	1190.54	1197.32
Log-logistic	--	--	1190.91	1197.69

Abbreviations: AIC, Akaike Information Criteria; ATC, average treatment effect of the control; ATT, average treatment effect of the treated; BIC, Bayesian Information Criteria; STC, simulated treatment comparison; UK, United Kingdom.

A.15.5 Retrospective chart review eligibility and exclusion criteria

Patients were selected for inclusion in the chart review based on the following eligibility criteria:

1. Aged ≥18 years
2. Diagnosis of mCSCC or laCSCC occurring between January 1, 2011 and December 31, 2015. Note To allow for an adequate potential follow up duration (retrospectively observed) of at least 24 months, the index date for mCSCC or laCSCC diagnosis had to fall between January 1, 2011 and December 31, 2015
3. Documented pathologic confirmation of mCSCC or laCSCC (i.e., biopsy confirmed)
4. CSCC medical history available from mCSCC or laCSCC diagnosis within the medical record for abstraction
5. For the metastatic cohort, patients were also required to have metastatic lesions at index (date of diagnosis) either local/regional nodal and/or distant

6. For the locally advanced cohort, patients with locally advanced disease and no evidence of metastases (e.g. M0 patients) at index date (date of diagnosis) were included if they had no evidence of additional surgery or radiation for recurrent CSCC in the same location during study period, and,
    a. If they use any systemic therapy for non-curative intent; systemic (IV or oral) therapies include chemotherapy, EGFR, other systemic agents, or,
    b. No evidence of additional treatment (e.g., best supportive care)

Exclusion criteria were also applied for patients who:

- Had enrolled in a clinical trial relating to CSCC therapy since diagnosis
- Had squamous cell carcinoma of the mucous membrane, of head and neck, of unknown origin
- Or were immunocompromised or immune at time of diagnosis with CSCC with the definition of immunocompromised assumed to be as for the EMPOWER-CSCC 1 trial:
    - Ongoing or recent (within last five years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments,
    - Had received immunosuppressive corticosteroid doses within four weeks of trial initiation,
    - Or had an active infection requiring therapy (i.e. human immunodeficiency virus).

In addition, locally advanced patients were excluded from the retrospective chart review if they had received surgery, RT or topical chemotherapy for the target lesion during study period or had confirmatory evidence of metastases.

Table 25: Data collection (patient characteristics and outcomes) for chart review based on protocol*

Category	Variables
Demographic data and baseline characteristics	• Age • Race • Ethnicity • Marital status • Tobacco use • Alcohol use • Vital status
Medical and surgical history	• Comorbidities
Diagnosis and prognostic factors	Patient status and key dates are collected: • Date of death • Date of most recent follow-up • Date of early stage diagnosis • Early diagnosis • Specialty of diagnosing physician Diagnostic and prognostic factors include: *At advanced diagnosis* • Type of lesion at advanced CSCC diagnosis • Primary tumour stage • Primary tumour diameter • Primary lesion location • Lymph node involvement • Distant metastasis • Infiltrative disease • Depth/thickness of primary lesion • Histologic tumour grade • Perineural invasion • Lymphovascular invasion *Not diagnosis date related* • Invasion beyond subcutaneous fat • ECOG performance status • Extra-dermal invasion (bone, cartilage, muscle, orbita) • Tumour invasion in base of skull or axial skeleton
Clinical outcomes	• Mortality (all cause/advanced CSCC related) and date of death • Overall survival • Progression and date of progression • Age at mCSCC or laCSCC diagnosis • Physician assessed best response
Health care resource utilisation	Key visits, dates and details are collected: • ER visits and number of visits • Hospital admissions, number of admissions and length of stay • ICU admissions • Number of visits: Medical oncologist, haematologist/oncologists, dermatologists, radiologists, ENT, oral and maxillofacial surgeon, clinical oncologist number of visits, other office visits • Start and end of pain management therapy • Did patient receive any pain management therapy since advanced diagnosis? • Pain management therapy administered (type, dose, frequency) Health care resource utilization includes (at advanced diagnosis and from advanced diagnosis): • Fine-needle aspiration cytology (FNAC) • Core biopsy • MRI • PET-CT scan • Excision biopsy (advanced diagnosis only) • Echocardiogram • Ultrasound

Category	Variables
	• 18F-fluorodeoxyglucose test • Regional node examination • Sentinel lymph node examination • PD-L1 expression testing • EGFR expression testing
Treatment patterns	Prior to advanced diagnosis: • Type and number of Surgical Procedures (all) • Radiation Therapy Not diagnosis date related: • Prescribing clinician type • First (second, third+) line of therapy • Duration of line of therapy • Administration form and frequency of administration • Dose, including dose changes and reason for changes • Number of planned and completed cycles • Reasons for discontinuing therapy • Dose delays including reason for delay
Adverse events	Grade 3 or 4 adverse events (CTCAE)

Notes:** * Additional elements were evaluated in the chart review audit, conducted Q4 2020 in the UK only and described in subsequent sections.* ***Abbreviations: *CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ENT, ear, nose & throat; ER, emergency department; FNAC, fine-needle aspiration cytology; ICU, intensive care unit; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; MRI, magnetic resonance imaging; PD-L1, programmed death-ligand 1; PET-CT, positron emission tomography – computed tomography.*

A.15.6 Retrospective chart review study audit (UK cohort)

An initial evaluation of median OS and PFS from patients in the UK cohort of the chart review who received at least one line of therapy post advanced diagnosis (n =) observed estimates which were longer than those available in published literature, particularly at earlier time points (see Figure 67; note this figure does not account for between study differences). The survival outcomes were shared with leading clinical experts who confirmed that the extended survival associated with a proportion of patients captured in this study was not in line with clinical expectations. In particular, survival times of patients in laCSCC were considered high compared to clinical expectation that survival in this population would not be expected to be beyond 2 years.

Figure 67: Comparison of overall survival estimates from the UK cohort (original data, received at least one line of therapy; n = [redacted] of the chart review and the cemiplimab studies

***Notes**: Cemiplimab Phase 2 trial using July 2021 DCO, cemiplimab Phase 1 trial updated using 2019 DCO. **Abbreviations**: OS, overall survival; SOC, standard of care; UK, United Kingdom*

Data review findings

An evaluation of the treatment and outcome patterns pointed to potential patient selection issues within the chart review, which may have driven the higher-than-expected survival estimates.

- There were significant gaps in treatment for some patients in the chart review data. Many patient records consisted of data with long periods of time with no event or no visit data, which appears contrary to standard treatment patterns for patients with advanced cancers
- Clinicians highlighted that the uptake of chemotherapy was proportionally higher than expected in this population, likely related to the chart review data collection. Clinical advice suggested that once patients have metastasized or

progressed following surgery/radiotherapy,there are no palliative treatments, so patients are cared for in the community (i.e. GPs) rather than hospitals. Data collection for the chart review did not capture records from communities and GPs where palliative patients are cared for. Furthermore, according to clinicians, patients receiving chemotherapy are generally fitter than those receiving BSC. This likely contributed to improved outcomes for these patients, alongside the benefit from systemic therapy itself.

- There was a lack of information on prior treatments. Common treatment patterns suggest very few patients are initially diagnosed with metastatic disease and thus they usually receive surgery or RT prior to advanced diagnosis, but the observed data showed only a minimal number with prior RT, surgery, or systemic therapy.
- A large proportion of the chart review population were indicated to have received palliative radiation and/or palliative surgery; however, dates of administration were not recorded and may have occurred prior to, during, or following systemic treatment. It is possible that some of these patients may have received regimens more akin to definitive rather than palliative RT, though this cannot be determined from the original data collection. In the UK cohort (as well as other European countries), the potential under-reporting of palliative treatments was quite significant and could have contributed to the overestimation of survival estimates.
- Review of the patient level data showed that deaths made up a significant portion of the PFS events in the chart review, despite these occurring well after cessation of therapy. Patients would be expected to progress prior to death, especially in the metastatic cohort, suggesting progression was not formally recorded in many charts.
- There were relatively few patients who experienced any events within the first six months of treatment. This is notable, as there are substantial numbers of patients that die within the first six months in EMPOWER-CSCC 1, as well as in all published literature on this patient population. This period of non-events could be due to the data collection process not being sufficiently comprehensive (it may be the case that not all events were recorded) or as patients enrolled in the chart review were generally healthier.

Study audit

Centre participation in the audit was optional, and of the [redacted] centres and 106 patients in the UK, [redacted] centres and [redacted] patients were audited. Additional data elements included in the audit but were not limited to: Reason why a patient was unresectable, confirmation of date of metastatic disease, location of metastases, baseline biopsy date and location, confirmation of additional biopsies, and reasons for radiation at baseline. Specifically, additional data elements were collected to understand why laCSCC patients were deemed not to be candidates for surgery or radiation and why these patients had extended survival compared to other published estimates in the same population.

The audit identified numerous laCSCC patients who had received excision biopsies both during and following systemic therapy. The reason for excision biopsies were not identified, but clinical expert opinion suggested these could be a form of tumour debulking which would render these patients incomparable to EMPOWER-CSCC 1 who were locally advanced, not eligible for surgery or RT. The administration of excision biopsies was concentrated across three centres, suggesting variation in practice in the UK.

A comparison of the baseline patient characteristics for the integrated cohort (n = [redacted]) and the subset of the audit cohort (n = [redacted]) who were integrated is presented in Table 26 and show that the patient characteristics are similar between the audit and integrated chart review cohort.

Table 26: Baseline patient characteristics in the UK integrated and audited chart review cohort

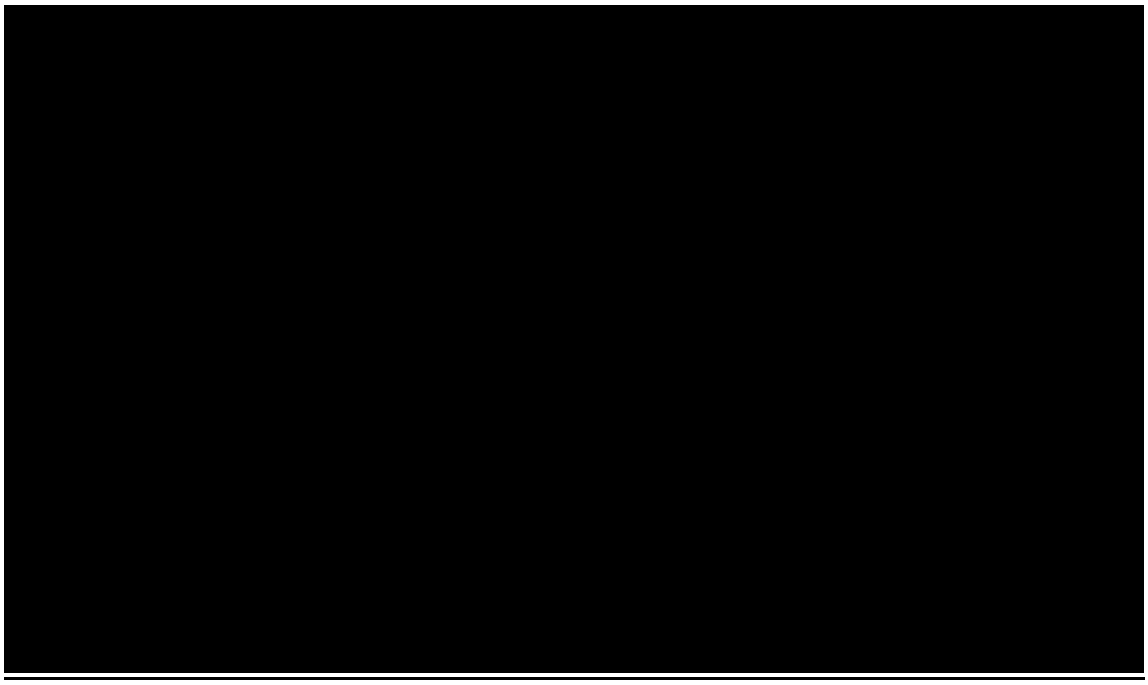
Characteristic		Chart review, integrated UK cohort	Chart review, audit UK cohort
N		[redacted]	[redacted]
Disease severity, n (%)	laCSCC, n (%)	[redacted]	[redacted]
	mCSCC	[redacted]	[redacted]
Age, median (range)		[redacted]	[redacted]
Gender, n (%)	Male	[redacted]	[redacted]
Differentiation, n (%)	Well	[redacted]	[redacted]
	Moderate/Poor/ Undifferentiated	[redacted]	[redacted]
	Undetermined	[redacted]	[redacted]

Characteristic		Chart review, integrated UK cohort	Chart review, audit UK cohort
Tumour location, n (%)	Head and Neck	[redacted]	[redacted]
	Trunk	[redacted]	[redacted]
	Extremities	[redacted]	[redacted]
T stage, n (%)	T0	[redacted]	[redacted]
	Tis	[redacted]	[redacted]
	Tx	[redacted]	[redacted]
	T1	[redacted]	[redacted]
	T2	[redacted]	[redacted]
	T3	[redacted]	[redacted]
	T4	[redacted]	[redacted]
ECOG performance status, n (%)	0[a]	[redacted]	[redacted]
	1[a]	[redacted]	[redacted]
Prior systemic therapy, n (%)		[redacted]	[redacted]
Prior radiation, n (%)		[redacted]	[redacted]

Note: a) measured from start of first line of therapy; b) prior radiation includes only those patients who have a confirmed date of administration – those patients in the chart review who were indicated to have received palliative radiation but with no date of administration defined have not been included in the count. Integrated audit population is the original chart review data combined with the audit.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; UK, United Kingdom.

A comparison of the overall survival estimates (integrated data [n = [redacted]]) from the chart review to CSCC trials and cemiplimab studies show that the chart review survival estimates are similar to overall survival as reported in the Jarkowski study which was used in the original submission to inform the chemotherapy comparator arm (see Figure 68).

Figure 68: Comparison of overall survival estimates from the UK cohort (integrated data [n =]), CSCC trials and cemiplimab studies



***Abbreviations**: CSCC, cutaneous squamous cell carcinoma; OS, overall survival; SOC, standard of care; UK, United Kingdom.*

A.15.7 Retrospective chart review - cohort inclusion decision rules

The decision rules were based on an analysis of the data and clinical expert opinion:
Decision Rule 1: The chart review collected survival data from UK patients treated with systemic (n =) and non-systemic therapy (n =). The population who did not receive systemic therapy were excluded from the analysis as:

- Some patients in the cohort received RT and/or surgery, however the intent of the treatment was not consistently recorded.
- There was no recorded treatment initiation date for BSC, there was no index from which to measure OS. Though it would be possible to measure OS for BSC from diagnosis, this measure would be different from those receiving systemic therapy at initiation of 1L therapy.

The exclusion of patients not receiving systemic therapy (n =) is considered conservative, as patients receiving BSC generally had poorer outcomes than those receiving systemic therapy

Decision Rule 2: In the TA592 submission for cemiplimab, experts considered that EGFR inhibitor data was not relevant to the NHS as these treatments are not licensed for use in the UK. Based on this, patients who did not receive platinum-based chemotherapy were excluded from the analysis (5-FU monotherapy n = [redacted], EGFR mono- or combination therapy n = [redacted], interferon alfa 2a mono- or combination therapy n = [redacted])

Decision Rule 3: Patients in the chart review could have ECOG performance scores greater than one at the initiation of their treatment, which was prohibited in the cemiplimab trials. To ensure comparability to the EMPOWER-CSCC 1 trial, patients in the chart review with ECOG performance scores >1 at treatment initiation were excluded from the analyses (n=[redacted]).

A.15.8 Retrospective chart review – Indirect treatment comparison

Methodologies considered for population adjustment

Based on guidance from NICE DSU 17, the following models were considered for use:[7]

- Naïve (unadjusted) comparison as a benchmark
- Adjusted comparison using IPW-average weighted treatment effect in the treated (ATT) models
- Adjusted comparison using IPW-average treatment effect in the controls (ATC) models

Average treatment effect in the treated (ATT)

ATT sets the cohort of treated patients as the reference (i.e. applying a weight of 1 to each patient in EMPOWER-CSCC 1/Study 1423), and the PS based weights were applied to the patients in the control group (i.e. chart review). Consequently, the weights were defined as:

$$w_i = Z_i + (1 - Z_i)\frac{e_i}{(1 - e_i)}$$

The reweighting of chart review patients effectively provides a means to obtain the treatment effect in a sample similar to the treated (i.e. EMPOWER-CSCC 1/Study 1423) population by up-weighing patients who are more similar to EMPOWER-CSCC 1/Study 1423 patients, and down-weighing patients who are dissimilar. In the

presence of extreme weights, trimmed weights, capping the value at the 95th percentile, were applied to reduce the variability of the estimated treatment effects. [9]

Note a model without individual weights provides a naïve estimate of the treatment effect, and a model with weights defined as above provides an estimate of the treatment effect in a population similar to EMPOWER-CSCC 1/Study 1423. As applying weights to create a new weighted chart review cohort induces within-patient correlations in outcomes, robust sandwich variances were computed to obtain 95% CI for the treatment effects.[16] Baseline characteristics for two studies were compared before and after applying weights to assess whether or not the propensity score based weights manage to balance baseline characteristics of the two populations as expected.

Covariate selection

A list of relevant covariates (prognostic factors) was identified through a targeted review and validated by clinical expert opinion.[8] Covariates considered for inclusion in the analysis were disease severity, age, gender, differentiation, tumour location, T stage, ECOG performance status, prior systemic therapy and prior radiation. Disease severity, age, gender and tumour location showed reasonable overlap between the three studies; however, differences were observed in differentiation and T stage, where the chart review included more patients with moderate/poor/undifferentiated tumours and T3, respectively. In addition, the Tis category for tumour staging was only observed in EMPOWER-CSCC 1. Little or no overlap was observed for ECOG performance status, prior systematic therapy and prior RT.

For the ATT models, prior systemic therapy could not be included in the analysis due to no patients having received prior systemic therapy in the chart review. The data quality for prior RT, specifically the dates of administration, was considered too poor to be used in any analysis and this variable was also excluded from the analysis. Given the prognostic importance of ECOG status, this variable was included in the full ATT model, despite the poor overlap, but was not included in ATT model 1 (model used in the base case analysis).

T stage was also split across three levels: T0/Tis/Tx/T1/T2, T3, and T4, as there was a higher proportion of patients in the chart review cohort with T stage 3/ 4 relative to other T stages compared with EMPOWER-CSCC 1 and Study 1423.

Indirect comparisons

Average treatment effect in the treated models

The model assessment process aimed to identify the model that provided the best weights and resulted in the highest improvement in the balance of the included covariates between EMPOWER-CSCC 1/Study 1423 and the chart review or the highest reduction in the magnitude of differences between all included covariates. The standardized difference was used to assess the extent of difference for each of the variables between the two populations. Three diagnostic measures were used to select the model with the best overall fit:

1. The number of key covariates with an improved balance: the number of covariates with a reduced absolute standardized difference, to a value less than 10%, after applying weights
2. The number of variables with an improved absolute standardized difference
3. Overall measure of balance across the considered covariates (i.e. ECOG, disease severity, age, gender, differentiation, tumour location and T stage in the ATT analysis; balance for prior systemic treatment was only considered in the ATC analysis): the difference of the absolute standardized difference for each of these covariates before and after applying weights were summed.

Note - the first and second measure were used in addition to the last diagnostic measure to ensure an improved balance of key covariates between EMPOWER-CSCC 1/Study 1423 and the chart review. The plot of absolute standardized difference for unweighted data, weighted data, and data with trimmed weights (capping the value at the 95th percentile) were used to assess the impact of extreme weights and select the final propensity score model with weights that resulted in the best balance of the key relevant covariates. Ten models with the best overall measure of improvement were selected based on the three diagnostic measures mentioned above; the effective sample size (ESS) was calculated and described for each IPW analysis.[16]

Average treatment effect in the controls models (ATC)

Sensitivity analyses were conducted matching the trial data to the integrated chart review data (ATC). The sensitivity analysis was conducted as the trial data had more variability in ECOG, prior systemic therapy, and T stage as well as a higher sample size. The proportion of patients for these characteristics was close to 0% (or 100%) in the integrated UK cohort (e.g., 0% of the chart review patients received prior systemic therapy), which implies that there were no (or too few) patients in the chart review with these characteristics that could have been up or down weighted to match for these variables. In terms of the matching variables, four ATC sensitivity analyses were conducted:

1. Matching using a full propensity score model, including all variables included in the ATT model plus prior systemic therapy, which could not be included in the ATT analyses due to the insufficient number of patients that received prior systemic therapy in the chart review data.
2. Matching using the best fitting model for the ATC analysis, starting with all covariates (except prior radiation) and selecting the matching variables based on the methodology as used in the ATT analysis
3. Matching using the full propensity score model as implemented for the ATT analysis
4. Matching using the best fitting propensity score model in the ATT analysis

The first two analyses leveraged the full data from the cemiplimab trials (i.e., allowing for matching of more variables), while analyses 3 and 4 allowed for a comparison of the ATT and ATC analyses. Note that a limitation of this scenario analysis concerns the representativeness and generalizability of the reweighted patient population. The ATC analysis simulates a patient population that resembles the chart review patients, while the baseline patient characteristics in the chart review have poor face-validity as described. For instance, the chart review patients were reported to have received no/limited treatment before the diagnosis of advanced disease.

Results of indirect comparison

Overview of indirect comparisons

Table 27 presents an overview of the results for the full and best fitting models for the ATC and ATT analyses, and the naïve (unadjusted) results as a benchmark. The table also shows the prognostic factors included in each analysis.

Without adjusting for differences between the populations, the (naïve) HR was [redacted]. The HR point estimates ranged from [redacted] (full ATC model) to [redacted] (best fitting ATC model 1). The range was smaller when comparing the trimmed HRs; these ranged from [redacted] to [redacted] in the best fitting ATC model 1 and full ATT model, respectively.

The observed ESS values in the IPW analyses are low, which are caused by the extreme weights. The ESS in the ATT analyses concerns the chart review cohort and the ESS in the ATC analyses concerns the ESS of the cemiplimab trials. In the trimmed analysis, the ESS values were generally higher and the point estimates of the HRs similar for the best fitting models. The HRs from the ATT analyses had narrower CIs than those from the ATC analyses, although the ESS was lower. This can be explained by the fact that in the ATT analyses, the chart review analysis cohort was matched to the cemiplimab trials and, therefore, when estimating the HR, the [redacted] patients from the cemiplimab trials were included in the analysis as well (in comparison to just the [redacted] patients from the chart review in the ATC analyses). It is important to highlight that the matching for the ATT analyses did not incorporate prior systemic treatment. As such, the balance in the ATT analyses may be an overestimate relative to the balance in the ATC analysis, which did incorporate this variable.

Table 27: Overview of indirect comparisons

	Full ATT	ATT 1	Full ATC	ATC 1	Naïve[a]
HR[c] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR[c] (95% CI) trimmed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Balance[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS trimmed[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Characteristic incorporated					
Disease severity (laCSCC, mCSCC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Full ATT	ATT 1	Full ATC	ATC 1	Naïve[a]
HR[c] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR[c] (95% CI) trimmed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Balance[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS trimmed[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Characteristic incorporated					
Differentiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour location (H&N, trunk, extremities)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T stage (TNM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: *1= best fitting propensity score model; a) the naïve model only included treatment as covariate; c) hazard ratios (HR) are cemiplimab vs chemotherapy; d) balance was based on the not-trimmed results; e) the ESS is the ESS for the trial in the ATC analyses and for the chart review for ATT analyses; f) trimmed patients were not excluded, however, their weight was set at the weight observed at the 95th percentile.* ***Abbreviations:*** *ATC, average treatment effect of the control; ATT, average treatment effect of the treated; CI, confidence interval; ESS, effective sample size; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck; HR, hazard ratio; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; MVR, multivariable regression; N, no; NA, not applicable; NP, not possible; T (TNM), T stage of the TNM Classification of Malignant Tumors; Y, yes.*

ATT (model base case)

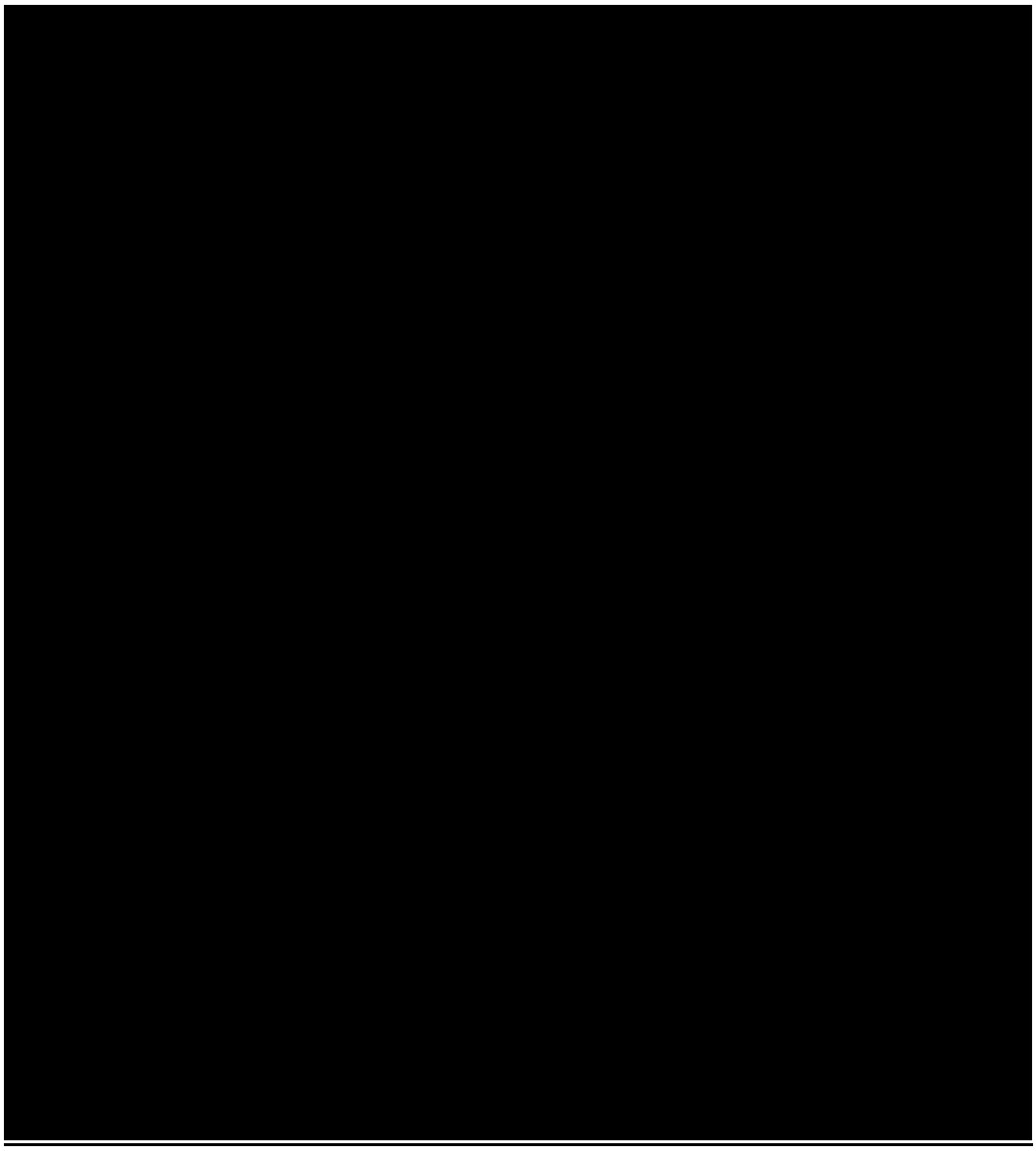
Table 28 presents the balance, ESS and trimmed ESS for ATT models 1-5, HRs and presents the matching variables included in each model. The HRs were similar across the best fitting ATT models ([redacted]) but the CI was much wider for the full models, which relates to low ESS and extreme weights. As noted in the main text, trimming had a limited impact on the HRs but improved the ESS.

Table 28: Overview of ATT analyses: full model, models 1-5 and naïve (unadjusted comparison)

	1	2	3	4	5	full	Naïve [a]
HR[b] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR[b] (95% CI) trimmed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Balance[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS trimmed[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Characteristic incorporated							
Disease severity (laCSCC, mCSCC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Differentiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour location (H&N, trunk, extremities)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T stage (TNM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: *a) the naïve model only included treatment as covariate; b) hazard ratios (HR) are cemiplimab vs chemotherapy; c) balance was based on the not-trimmed results; d) ESS is equal to the number of patients after reweighting for the trial for ATC analyses and for the chart review for ATT analyses; e) trimmed patients were not excluded, however, their weight was set at the weight observed at the 95th percentile.* ***Abbreviations:*** *ATT, average treatment effect of the treated; CI, confidence interval; ESS, effective sample size; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck; HR, hazard ratio; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; N, no; NA, not applicable; NP, not possible; T (TNM), T stage of the TNM Classification of Malignant Tumours; Y, yes*

Figure 69: Kaplan–Meier curves full ATT model: weighted (above) and trimmed (below)



Abbreviations: *ATT, average treatment effect of the treated; NA, not applicable; PBC, platinum-based chemotherapy*

Average treatment effect in the controls analyses (ATC)

Table 29 presents the unadjusted and reweighted patients characteristics in the ATC analyses for the full ATC model and ATC model 1, which was the best fitting ATC model. The sample size in the ATC analysis, defined as the sum of weights, differed significantly from the original sample size in the trials and dropped from [redacted] in the full ATC model. This was caused by a large proportion of patients getting a weight equal to zero due to matching for ECOG and prior systemic treatment. Some

differences in patient characteristics were observed amongst the reweighted ATC models and the chart review analysis cohort.

Table 29: Unadjusted and reweighted baseline patient characteristics

Characteristic		Cemiplimab trials[a] (unadjusted)	Cemiplimab (reweighted - full ATC model)	Cemiplimab (reweighted - ATC model 1)	Chart review (unadjusted)
N[b]		219.0	[redacted]	[redacted]	[redacted]
Disease severity, n (%)	laCSCC, n (%)	88.0 (40.2)	[redacted]	[redacted]	[redacted]
	mCSCC	131.0 (59.8)	[redacted]	[redacted]	[redacted]
Age, mean (sd)		71.2 (11.2)	[redacted]	[redacted]	[redacted]
Gender, n (%)	Male	182.0 (83.1)	[redacted]	[redacted]	[redacted]
Differentiation, n (%)	Well	[redacted]	[redacted]	[redacted]	[redacted]
	Moderate/Poor/ Undifferentiated	[redacted]	[redacted]	[redacted]	[redacted]
	Undetermined	[redacted]	[redacted]	[redacted]	[redacted]
Tumour location, n (%)	Head and Neck	[redacted]	[redacted]	[redacted]	[redacted]
	Trunk	[redacted]	[redacted]	[redacted]	[redacted]
	Extremities	[redacted]	[redacted]	[redacted]	[redacted]
T stage (TNM), n (%)	T0	[redacted]	[redacted]	[redacted]	[redacted]
	Tx	[redacted]	[redacted]	[redacted]	[redacted]
	T1	[redacted]	[redacted]	[redacted]	[redacted]
	T2	[redacted]	[redacted]	[redacted]	[redacted]
	T3	[redacted]	[redacted]	[redacted]	[redacted]
	T4	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)	0	96.0 (43.8)	[redacted]	[redacted]	[redacted]
	1	123.0 (56.2)	[redacted]	[redacted]	[redacted]
Prior systemic therapy, n (%)		80.0 (36.5)	[redacted]	[redacted]	[redacted]
Prior radiation, n (%)		[redacted]	[redacted]	[redacted]	[redacted]

Notes: *a) EMPOWER-CSCC 1 and Study 1423 pooled; b) for the adjusted models N is equal to the sum of weights.*
Abbreviations: *ATC, average treatment effect on control; ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; NA, not applicable; sd, standard deviation; T (TNM), T stage of the TNM Classification of Malignant Tumours*

Table 30 shows that HRs differed slightly amongst the best fitting ATC models ([redacted]), however, the full model estimated a more extreme effect (HR [redacted]). The HR of the weighted and trimmed ATT analysis 1 was similar ([redacted]), while the trimmed analysis had a higher ESS.

Table 30: Overview of the ATC analyses: full model, models 1-5 and naïve (unadjusted) comparison

	1	2	3	4	5	full	Naïve[a]
HR[b] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR[b] (95% CI) trimmed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Balance[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS trimmed[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Characteristic incorporated							
Disease severity (laCSCC, mCSCC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Differentiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour location (H&N, trunk, extremities)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T stage (TNM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: *a) the naïve model only included treatment as covariate; b) hazard ratios (HR) are cemiplimab vs chemotherapy; c) balance was based on the not-trimmed results; d) ESS is equal to the number of patients after reweighting for the trial for ATC analyses and for the chart review for ATT analyses; e) trimmed patients were not excluded, however, their weight was set at the weight observed at the 95th percentile.* ***Abbreviations:*** *ATC, average treatment effect of the control; CI, confidence interval; ESS, effective sample size; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck; HR, hazard ratio; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; N, no; NA, not applicable; NP, not possible; T (TNM), T stage of the TNM Classification of Malignant Tumours; Y, yes.*

A comparison of the ATC sensitivity analyses compared to the ATT analyses are presented in Table 31. Differences in the estimated treatment effects were observed even in models including the same covariates. For instance, the full ATT model estimated a HR of [redacted] while the ATC analysis that adjusted for the covariates included in the full ATT model estimated a HR of [redacted]. This implies that differences between the ATT and ATC analyses were partly explained by differences in the underlying populations.

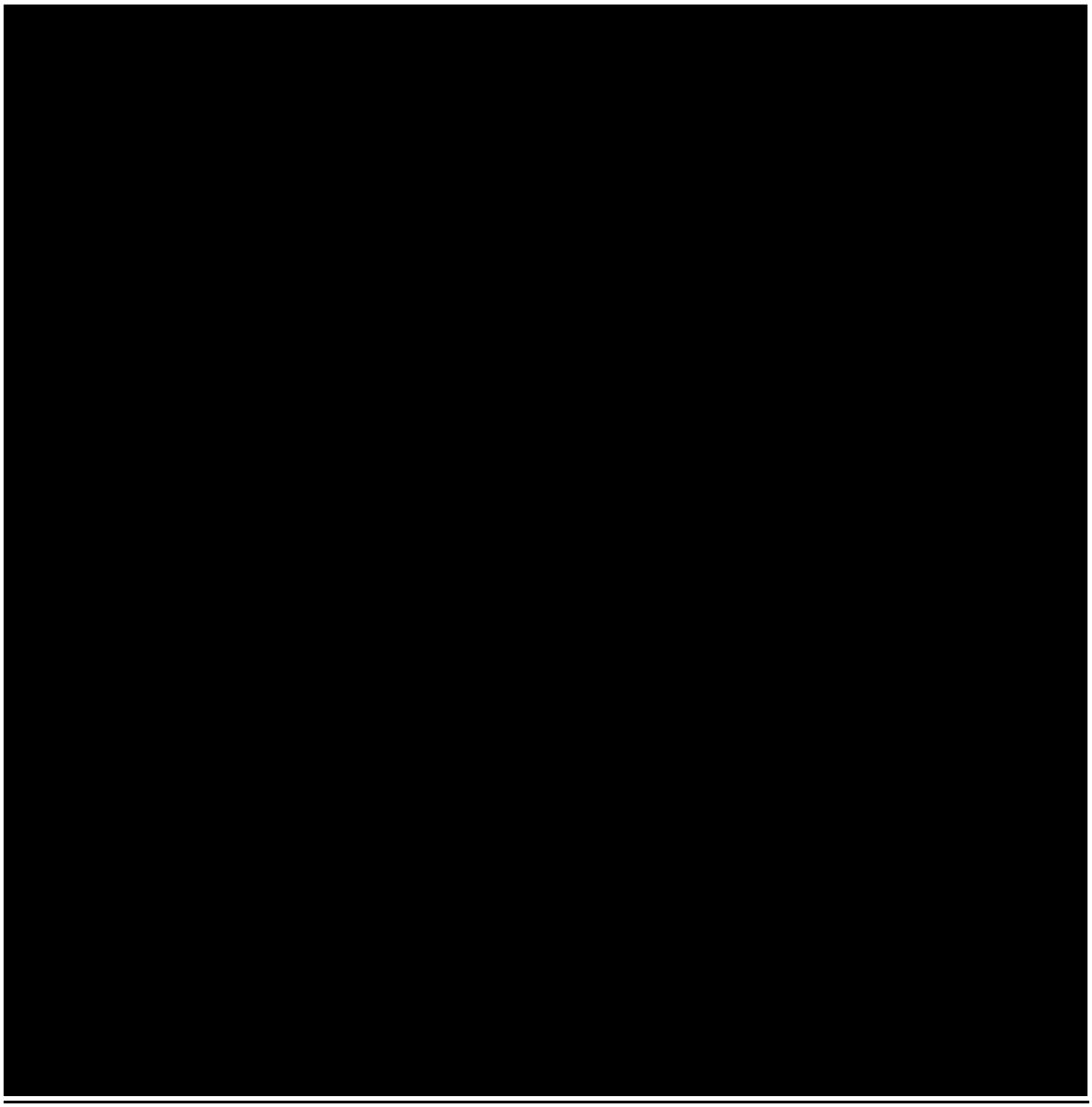
Table 31: ATC sensitivity analyses and results of ATT and ATC models for comparison

	ATT analysis: full ATT	ATC analysis: full ATT model	ATC analysis: full ATC model	ATT analysis: ATT model 1	ATC analysis: ATT 1	ATC analysis: ATC 1
HR[a] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR[a] (95% CI) trimmed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Balance[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESS trimmed[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Characteristic incorporated						
Disease severity (laCSCC, mCSCC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Differentiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour location (H&N, trunk, extremities)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T stage (TNM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: *a) hazard ratios (HR) are cemiplimab vs chemotherapy; b) balance was based on the not-trimmed results; c) ESS is equal to the number of patients after reweighting for the trial for ATC analyses and for the chart review for ATT analyses; d) trimmed patients were not excluded, however, their weight was set at the weight observed at the 95th percentile.*
Abbreviations: *ATC, average treatment effect of the control; ATT, average treatment effect of the treated; CI, confidence interval; ESS, effective sample size; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck; HR, hazard ratio; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; N, no; NA, not applicable; NP, not possible; T (TNM), T stage of the TNM Classification of Malignant Tumours; Y, yes.*

The KM curves for the naïve, weighted and trimmed results for the full model and model 1 of the ATC analyses are presented in Figure 70 and Figure 8.

Figure 70: Kaplan–Meier curves full ATC model: weighted (above) and trimmed (below)



A.15.9 Sun 2019 and Jarkowski 2016: Indirect treatment comparison

Overview of analysis

The reported KM curves in Jarkowski 2016 and Sun 2019 were digitized (DigitizeIt; http://www.digitizeit.de/). The algorithm proposed by Guyot et al., 2011 was then applied to reconstruct IPD i.e. survival and censoring times for each intervention group.[17] In addition to an unadjusted comparison, where the reconstructed IPD and observed outcomes from the study were compared to the observed data from the

cemiplimab trials, we used two different methods to adjust for the difference in baseline characteristics, thereby generating estimates of what the comparator OS and PFS would have been if cemiplimab had been included as a comparator in the trials/studies: simulated treatment comparison (STC) and MAIC.

In the STC, the regression models were first fitted to the IPD from the cemiplimab trials in order to estimate the outcomes of interest as a function of the different combinations of prognostic factors. The best fitting models (determined from the AIC) were then used to predict outcomes for cemiplimab in each of the populations observed in the comparator studies, and these predicted cemiplimab “arms” were compared to the outcomes from each study separately. Bootstrap samples were used to estimate the standard errors of the predicted survival outcomes. For the MAIC, patients that would not have been eligible for inclusion in the comparator study based on inclusion and exclusion criteria were first removed from the sample. A logistic regression incorporating a propensity score i.e. the probability of being enrolled in one study versus the other was then used to estimate weights for the IPD so that their mean characteristics matched those from the target populations in each of the comparator studies. These weights were incorporated into the estimation of treatment effects. Note there is no statistic similar to AIC which can be used to compare the fit of different MAIC models, therefore model selection was based solely on the STC.

In the STC, the regression models were first fitted to the IPD from the cemiplimab trials in order to estimate the outcomes of interest as a function of the different combinations of prognostic factors. The best fitting models (determined from the AIC) were then used to predict outcomes for cemiplimab in each of the populations observed in the comparator studies, and these predicted cemiplimab “arms” were compared to the outcomes from each study separately. Bootstrap samples were used to estimate the standard errors of the predicted survival outcomes. For the MAIC, patients that would not have been eligible for inclusion in the comparator study based on inclusion and exclusion criteria were first removed from the sample. A logistic regression incorporating a propensity score i.e. the probability of being enrolled in one study versus the other was then used to estimate weights for the IPD so that their mean characteristics matched those from the target populations in each

of the comparator studies. These weights were incorporated into the estimation of treatment effects.

Simulated treatment comparisons

The STC involved creating a regression model for the index population (i.e. those treated with cemiplimab) and modelling the outcome of interest as a function of relevant patient-related factors for pooled IPD from EMPOWER-CSCC 1/Study 1423. The regression model was then used to predict the outcomes for the cemiplimab treated population that would have been observed in populations from comparator studies (i.e. the target population) for which only aggregate study-level data were available. To do this, covariate values were centred at the mean of the target trial, thereby giving a regression coefficient for treatment that represented the average treatment difference between the target and index populations. In theory, if the regression model includes all of the unbalanced prognostic factors and effect modifiers, then the resulting treatment effect estimate will be unbiased. The cemiplimab arm was estimated for an compared to each individual single arm trial featuring a comparator of interest using the regression model for time-to-event outcomes as a function of relevant covariates using IPD was developed using the Cox proportional hazards framework for time-to-event outcomes and the logistic model for dichotomous outcomes.

As noted, a MAIC was conducted as a sensitivity analysis. In this analysis, a propensity score weight was used to adjust for differences between the index trial(s) (i.e. pooled data from EMPOWER-CSCC 1) and the target population in each relevant comparator single arm clinical trial/observational study by increasing the weight of individuals with more similar patient-related factors. Hazard ratios were calculated using a Cox proportional hazards regression incorporating the weights produced and new ESS after matching the cemiplimab data to each of the external trial populations.

Covariate selection

The covariates included in the core model and in the extended model depended on the availability of data on prognostic factors reported in EMPOWER-CSCC 1, Study 1423 and the Sun 2019 study. Those considered but had insufficient data to support

including in the analysis included: Immune status (immunocompromised patients were excluded from the cemiplimab trials so this could not be adjusted for), tumour grade, tumour depth and perineural invasion.

Table 32 presents the prognostic factors included in the core models. The study by Jarkowski, which was used in TA592 is also presented. It should be noted that more prognostic factors including ECOG PS, tumour location and prior radiation therapies were reported in the Sun et al. study for use in the analysis compared to Jarkowski 2016.

Table 32: Baseline characteristics for prognostic factors included in the core and extended models for each trial in the analysis.

Prognostic factor		Pooled EMPOWER-CSCC 1 and Study 1423 (n = 219)	Jarkowski et al. 2016[a] (n = 25)	Sun et al. 2019[b] (n = 32)
Core model				
Disease stage, n (%)	**laCSCC**	88 (40.2)	13 (72)[a]	16 (50)
	mCSCC	131 (59.8)	5 (28)[a]	16 (50)
Age, median (range)		72 (38-96)	66.4 (2.8)[c]	73 (43-89)
Tumour grade	**Well differentiated**	43 (19.6)	--	--
	Moderate/poorly differentiated	145 (66.2)	--	--
Tumour location	**Head and neck**	150 (68.5)	11 (44)[d]	32 (100)
	Trunk	27 (12.3)	7 (28)[d]	0 (0)
	Extremities	45 (20.5)	3 (12)[d]	0 (0)
T stage	**T3/4**	67 (30.1)	--	11 (40.6)
	Other	152 (69.4)	--	19 (59.4)
Additional covariates in extended model				
Male, n (%)		182 (83.1)	18 (72)	26 (81.3)
ECOG PS	**0**	96 (43.8)	--	0(0)
	1	123 (56.2)		32 (100)
	2 or above	0 (0)		
Prior systemic therapies		80 (36.5)	≤ 8 (32)	--
Prior radiation therapies		152 (69.4)[e]	--	32 (100)

Notes: a) *Proportions among the chemotherapy with platinum subgroup (n = 18);* ***b)*** *Patient characteristics were reported for the 32 immunocompetent patients in Sun et al. 2019; characteristics were not reported separately for the target population in that study (i.e. 20 immunocompetent patients with lesions that were not amenable to surgery);* ***c)*** *Reported as mean and standard error;* ***d)*** *Two patients had lesions on the genital area, and two patients had unknown tumour locations.* ***e)*** *Data on prior radiation therapy was not available for individual patients from Study 1423.* ***Abbreviations:*** *CSCC, cutaneous squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance score; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC.*

A.15.10 Quality of Life data

Further EMPOWER -CSCC 1 health related quality of life data were collected up to the October 2020.

As per TA592, updated health state utility values were derived from statistical analysis of the EORTC QLQ-C30 data in EMPOWER-CSCC 1 (October 2020 data cut) converted to EQ-5D-3L values using the Longworth et al. (2014) mapping algorithm, in line with the National Institute for Health and Care Excellence (NICE) reference case (see detail on mapping below).

The utility values from the latest EMPOWER data cut (October 2020 data cut) are presented alongside utility values used in NICE TA592 (October 2017 data cut) in Table 33.

Table 33: Utility estimates used in the base case cost-effectiveness analysis

Health state	October 2017 data cut		October 2020 data cut	
	Mean	SE	Mean	SE
Longworth et al. (2004) algorithm				
Pre-progression	0.793	0.017	[redacted]	[redacted]
Post-progression	0.701	0.022	[redacted]	[redacted]
Key: SE, standard error.				

SE Standard error

Utility values calculated using the latest EMPOWER data cut are broadly comparable to those from the October 2017 EMPOWER-CSCC 1 data cut used in the CDF entry cost-effectiveness model (TA592). The October 2020 pre-progression health state shows a small decrease in utility when compared with the October 2017 pre-progression utility; the post-progression utility is similar across data cuts. The trend in utility values is maintained; the post-progression health state is associated with a lower utility than the pre-progression health state.

Utility mapping

EORTC QLQ-C30 data collected from EMPOWER-CSCC 1 was mapped to the preference-based Euroqol-5 dimension 3-level (EQ-5D-3L) instrument to derive a utility for the pre- and post-progression health states by applying an established regression algorithm to the IPD from EMPOWER-CSCC 1. The same approach for the resubmission was adopted as for the initial submission, whereby base case utilities were estimated using the Longworth 2014 algorithm, which was selected based on its predictive ability for population encompassing multiple cancer types.[18]

UK specific tariffs were applied to estimate country-specific utilities. A sensitivity analysis was performed using the algorithm from McKenzie 2009, which was also identified in the literature review as having good predictive qualities.[19] Note the mapping analyses was conducted using the October 2020 DCO of EMPOWER-CSCC 1 and was not updated for the purposes of this analysis, as there was no additional quality of life data collected between the October 2020 and July 2021 DCOs.

A.15.11 Safety data

Further EMPOWER study CSCC 1 safety data were collected up to the July 2021 DCO. The adverse event rates from the latest EMPOWER-CSCC 1 DCO (July 2021) are presented alongside rates used in the original submission (October 2017 DCO) in Table 34.

Table 34: Adverse event rates applied for cemiplimab

Adverse event	October 2017 data cut		July 2021 data cut	
	Point estimate	Standard error	Point estimate	Standard error
Skin infection	1.08%	0.88%	[redacted]	[redacted]
Hypercalcaemia	2.10%	1.22%	[redacted]	[redacted]
Failure to thrive	7.70%	5.44%	[redacted]	[redacted]
Fatigue	1.80%	1.80%	[redacted]	[redacted]
Hypokalaemia	1.80%	1.26%	[redacted]	[redacted]
Anaemia	0.90%	0.89%	[redacted]	[redacted]
Source: Sanofi data on file, 2018.				

Differences in adverse event rates for failure to thrive and fatigue between the 2017 and 2021 data cuts are due to corrections made to the cost-effectiveness model post submission (see Appendix A.15.12 for more detail).

Updated EMPOWER adverse event rates (July 2021) are broadly comparable to those from the CDF entry cost-effectiveness model used in the original appraisal (October 2018). The latest data cut shows a small increase in anaemia and skin infection adverse event (AE) rates and a small decrease in hypercalcaemia and hypokalaemia AE rates.

A.15.12 Cost-effectiveness model parameters

Table 35: Summary of variables applied in the economic model

Variable		NICE TA592				CDF resubmission			
		Base case value	Low value	High value	Distribution	Base case value	Low value	High value	Distribution
Patient characteristics at baseline									
Percentage male (%)		85.0%	Not varied in sensitivity analysis			83.1%	Not varied in sensitivity analysis		
Age (years)		70.44	Not varied in sensitivity analysis			71.16	Not varied in sensitivity analysis		
Males	Weight (kg	83.9	Not varied in sensitivity analysis			83.7	Not varied in sensitivity analysis		
	Height (cm)	174.7	Not varied in sensitivity analysis			175.2	Not varied in sensitivity analysis		
Females	Weight (kg)	62.1	Not varied in sensitivity analysis			66.2	Not varied in sensitivity analysis		
	Height (cm)	158.6	Not varied in sensitivity analysis			160.3	Not varied in sensitivity analysis		
PFS and OS parameters									
PFS and OS		The shape and scale parameters are randomly drawn from the PFS and OS coda samples based on 1,000 iterations from the Markov Chain Monte Carlo (MCMC) for the scale and corresponding shape parameters for each relevant scenario.				For consistency with the original submission, one thousand sets of shape and scale parameters are randomly drawn from the PFS and OS joint distributions of the scale and shape parameters for each relevant scenario.			
Adverse event rates for Cemiplimab									
Anaemia		0.009	0.000	0.033	Beta	0.041	0.018	0.075	Beta
Failure to thrive		0.077	0.008	0.213	Beta	[redacted]	[redacted]	[redacted]	-
Fatigue		0.018	0.002	0.050	Beta	-	-	-	-
Hypercalcaemia		0.021	0.004	0.051	Beta	[redacted]	[redacted]	[redacted]	Beta
Hypokalaemia		0.018	0.002	0.050	Beta	[redacted]	[redacted]	[redacted]	Beta
Neutropenia		-	-	-	-	[redacted]	[redacted]	[redacted]	Beta
Skin infection		0.011	0.001	0.033	Beta	[redacted]	[redacted]	[redacted]	Beta
Adverse event rates for chemotherapy									
Anaemia		0.145	0.106	0.189	Beta	0.145	0.106	0.189	Beta

Variable	NICE TA592				CDF resubmission			
	Base case value	Low value	High value	Distribution	Base case value	Low value	High value	Distribution
Febrile neutropenia	0.052	0.030	0.079	Beta	0.052	0.030	0.079	Beta
Hypokalaemia	0.071	0.045	0.103	Beta	0.071	0.045	0.103	Beta
Neutropenia	0.326	0.266	0.390	Beta	0.326	0.266	0.390	Beta
Stomatitis or oral mucositis	0.086	0.057	0.120	Beta	0.086	0.057	0.120	Beta
Thrombocytopenia	0.077	0.050	0.110	Beta	0.077	0.050	0.110	Beta
Utilities								
Progression-free survival	0.793	0.469	0.980	Beta	0.768	0.740	0.794	Beta
Post-progression survival	0.701	0.312	0.963	Beta	0.707	0.665	0.747	Beta
Adverse event utility decrements								
Anaemia	0.006	0.005	0.007	Beta	0.006	0.005	0.007	Beta
Failure to thrive	0.006	0.005	0.007	Beta	-	-	-	-
Fatigue	0.006	0.005	0.007	Beta	-	-	-	-
Febrile neutropenia	0.008	0.006	0.009	Beta	0.008	0.006	0.009	Beta
Hypercalcaemia	0.007	0.006	0.009	Beta	0.007	0.006	0.009	Beta
Hypokalaemia	0.007	0.006	0.009	Beta	0.007	0.006	0.009	Beta
Neutropenia	0.007	0.006	0.009	Beta	0.007	0.006	0.009	Beta
Skin infection	0.010	0.008	0.012	Beta	0.010	0.008	0.012	Beta
Stomatitis or oral mucositis	0.013	0.010	0.015	Beta	0.013	0.010	0.015	Beta
Thrombocytopenia	0.009	0.007	0.011	Beta	0.009	0.007	0.011	Beta
Monthly administration costs								
Cemiplimab	252.01	205.05	303.75	gamma	331.67	269.86	399.76	gamma
Cisplatin + 5FU	1,143.19	1094.32	1193.11	gamma	1,588.88	1,524.53	1,654.54	gamma
Monthly drug acquisition costs								
Cemiplimab	4,571.12	Not varied in sensitivity analysis			4,571.12	Not varied in sensitivity analysis		
Cisplatin + 5FU	40.90	Not varied in sensitivity analysis			40.90	Not varied in sensitivity analysis		

Variable	NICE TA592				CDF resubmission			
	Base case value	Low value	High value	Distribution	Base case value	Low value	High value	Distribution
Resource use frequencies in progression-free health state								
Palliative surgery	1	The values of these parameters were not varied in the sensitivity analysis as it was the cost associated with these that was actually varied to reflect the uncertainty in both these parameters the costs.			1	The values of these parameters were not varied in the sensitivity analysis as it was the cost associated with these that was actually varied to reflect the uncertainty in both these parameters the costs.		
Oncologist visit	2				2			
GP visit	1				1			
Blood test	2				2			
Nurse wound management (community nurse)	10				10			
Wound dressings	10				10			
Nurse tissue viability	1				1			
Clinical nurse specialist	1				1			
Palliative RT	0.3				0.3			
Complex palliative RT	0.3				0.3			
Resource use frequencies in post-progression health state								
Palliative surgery, following treatment	1	The values of these parameters were not varied in the sensitivity analysis as it was the cost associated with these that was actually varied to reflect the uncertainty in both these parameters the costs.			1	The values of these parameters were not varied in the sensitivity analysis as it was the cost associated with these that was actually varied to reflect the uncertainty in both these parameters the costs.		
GP visit	2				2			
Nurse wound management (community nurse)	12				12			
Wound dressings	12				12			
Nurse tissue viability nurse	2				2			
District nurse	1				1			
Palliative RT	0.3				0.3			
Complex palliative RT	0.3				0.3			
One-time costs progression-free survival								
Applied for all therapies	27.55	22.42	33.21	gamma	28.78	23.42	34.69	gamma

Variable	NICE TA592				CDF resubmission			
	Base case value	Low value	High value	Distribution	Base case value	Low value	High value	Distribution
Monthly costs progression-free survival								
Applied for all therapies	1,011.61	823.08	1,219.28	gamma	687.42	1,010.25	1,496.54	gamma
One-time cost post-progression survival								
Applied for cemiplimab	7,650.53	6,224.78	9,221.10	gamma	6,825.00	5,553.10	8,226.11	gamma
Applied for chemotherapy and BSC	7,642.08	6,217.90	9,210.92	gamma	6,816.18	5,545.92	8,215.47	gamma
Monthly costs post-progression survival								
Applied for all therapies	805.84	655.66	971.27	gamma	1,092.89	889.22	1,317.24	gamma
Adverse event costs								
Anaemia	1,273.72	1,036.35	1,535.20	gamma	1,414.99	1,151.29	1,705.47	gamma
Failure to thrive	3,179.70	2,587.13	3,832.46	gamma	-	-	-	-
Fatigue	3,179.70	2,587.13	3,832.46	gamma	-	-	-	-
Febrile neutropenia	2,688.94	2,187.83	3,240.95	gamma	2,726.59	2,218.46	3,286.33	gamma
Hypercalcaemia	1,139.92	927.48	1,373.93	gamma	1,235.25	1,005.05	1,488.83	gamma
Hypokalaemia	1,139.92	927.48	1,373.93	gamma	1,235.25	1,005.05	1,488.83	gamma
Neutropenia	325.49	264.83	392.31	gamma	412.98	336.02	497.77	gamma
Skin infection	143.20	116.51	172.60	gamma	145.20	118.14	175.01	gamma
Stomatitis or oral mucositis	998.38	812.32	1,203.33	gamma	1,012.36	823.69	1,220.18	gamma
Thrombocytopenia	325.49	264.83	392.31	gamma	412.98	336.02	497.77	gamma
Other model parameters								
Model horizon	30 years	Only varied in scenario analyses			30 years	Not varied in sensitivity analysis		
Model cycle length	1 month	Not varied in sensitivity analysis			1 month	Not varied in sensitivity analysis		
Discount rate for costs	3.5%	Only varied in scenario analyses			3.5%	Not varied in sensitivity analysis		
Discount rate for benefits	3.5%	Only varied in scenario analyses			3.5%	Not varied in sensitivity analysis		

A.15.13 Cost-effectiveness model corrections and changes

The ERG corrected company base case model (ID1367 ERG corrected company base case_CAA price v0.1 08.01.19 (ACIC) was used as a base for the revised model for the CDF review submission. The following changes were made to ensure model transparency an ease of use:

Corrections:

- Amendment to only include adverse events which reached a >5% threshold
- General mortality corrected to be based on population specific split of gender (i.e. dynamic based on cemiplimab population selected)

Changes:

- Addition of EMPOWER-CSCC 1 ([redacted]month) KM data and parametric extrapolations for OS and PFS as an option in the 'Model Parameters' sheet
- Addition of EMPOWER-CSCC Safety and utility data ([redacted]month) to Library Safety Tx and Library Utility respectively
- Addition of new comparative evidence options for chemotherapy and BSC in the 'Model Parameters' sheet
- Removal of inactive tabs, formulas to streamline model
- New switches in the 'Model Parameters' sheet to allow for selection of data sources and model corrections
- Update of company base case settings in the 'Model Parameters' sheet

Additionally, a frequentist framework was fitted in the model to allow for the chart review ATT/ATC analyses. Whilst fitting the frequentist models, we noticed a discordance between the model fits to Jarkowski 2016 PFS between the Bayesian and frequentist frameworks. The KMs retrieved from this study only reported n at risk at the initial time point, and consequently the algorithm to reconstruct IPD had difficulties identifying the times of censored observations. Censored values were lumped at the tail end of the KM. For the initial submission (using the Bayesian framework), we redistributed the effect of censors for Jarkowski 2016 to improve fit of the parametric distributions to the data and this same approach has now been applied to the distributions fitted in the frequentist framework

A.15.14 Cost-effectiveness results (deterministic) – list price

Table 36: Cost-effectiveness results for cemiplimab versus chemotherapy (deterministic, list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (cemiplimab: log-normal for OS extrapolation, log-normal for PFS extrapolation, October 2017 EMPOWER-CSCC 1 data, *24-month stopping rule, ERG resource use costs,* CDF entry MAA, 36-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence (*cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data,* 24-month stopping rule, ERG resource use costs*, 60-month hazard switching assumption*; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost-effectiveness analysis 3: New company base case (cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 60-month hazard switching assumption; chemotherapy: *log-logistic for OS extrapolation, chart review*)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: CSCC, cutaneous squamous cell carcinoma; ERG, Evidence Review Group; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.								

Table 37: Cost-effectiveness results for cemiplimab versus BSC (deterministic, list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (cemiplimab: log-normal for OS extrapolation, October 2017 EMPOWER-CSCC 1 data, *24-month stopping rule, ERG resource use costs*, 36-month hazard switching assumption; BSC: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence (cemiplimab: *log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-*								

***CSCC 1 data*, 24-month stopping rule, ERG resource use costs, *60-month hazard switching assumption*; BSC: Gompertz for OS extrapolation, Jarkowski 2016)**								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 3: New company base case (cemiplimab: log-normal for OS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 60-month hazard switching assumption; BSC: *log-logistic for OS extrapolation, Sun 2019*)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: CSCC, cutaneous squamous cell carcinoma; ERG, Evidence Review Group; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.								

A.15.15 Clinical validation

Key modelling assumptions were validated with three clinicians at two 2-hour teleconference meetings on 1st December 2021. Dr Amarnath Challapalli (University Hospitals Bristol NHS Foundation Trust), Dr Grant Stewart (Royal Cornwall Hospitals Trust) and Dr Andrew Sykes (The Christie NHS Foundation Trust) were asked questions regarding the retrospective chart review data, expectations for sustained treatment benefit following treatment stopping, cemiplimab survival, progression-free survival and OS extrapolations and generalizability of SACT data. Meeting notes were written up and approved by the clinicians before being submitted with the questions asked and both are included in the reference pack.[5]

A.15.16 Systematic literature review

One additional study for cemiplimab was identified via the updated systematic literature review conducted on 17 July 2021, however it is from a French early access program and following a review of the study, Sanofi considered this data would not be appropriate (see below). Therefore, data from EMPOWER remains the primary source of data

The Hober et al 2021 study was conducted in France and so the treatment pathway and clinical practice differs from the UK, which could affect patient outcomes and therefore, the data from the Hober study may not be generalizable to UK patients. Moreover, a higher number of patients received systemic treatment before getting cemiplimab compared to EMPOWER-CSCC 1 (49% vs 34%). Hober reported 38% of patients being treated with EGFR plus chemotherapy prior to treatment with cemiplimab; EGFR treatments are not available for CSCC patients in the UK. The population in Hober comprised of 24% immunocompromised patients and 27% had an ECOG PS ≥ 2, whereas the cemiplimab trials did not include immunocompromised patients and only included patients with ECOG 0-1. Hober has not been explored within the economic model or within this submission given it is a non-UK study and the populations are not generally comparable.[20]

The updated systematic literature review can be provided upon request.

A.16 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592)

Clarification questions

January 2022

File name	Version	Contains confidential information	Date
ID3883 Clarification questions response Sanofi Final (v4.0)_AIC CIC MARKED 20220511	Final (v4.0)	Yes	11th May /2022

Notes for company

Highlighting in the template

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Supplementary Materials:

- REG33960 Cemiplimab CSCC SLR TR
- TA592_Cemiplimab_final_report_draft_CONFIDENTIAL_v4
- MDA_cSCC_Pt_CRF__laCSCC MAIN STUDY_16JAN2018
- MDA_CSCC_Pt_CRF__mCSCC MAIN STUDY_24APR2018
- UK CSCC PT FOLLOW-UP CRF 1 OCT 2020 FINAL
- CSCC Chart Review Study Protocol FINAL 17DEC2017_rev 04Jan2018 (with Italy)
- ID3883 NICE CDF exit Clarification Question A17
- ID3883 NICE CDF exit ERG Clarification Questions - Section B

Section A: Clarification on effectiveness data

Systematic literature review

A1. CS section A.15.16 states that the updated systematic literature review can be provided upon request. Please provide this, including the list of excluded studies with the reasons for exclusion.

Sanofi response:

The updated technical report for the systematic literature review (SLR) (“REG33960 Cemiplimab CSCC SLR TR”) is included within the supplementary materials attached to the Clarification response.

Table 1 presents the list of studies excluded at full-text screening from the SLR update (July 2021) and the original SLR (April 2019).

Table 1: Studies excluded at full-text screening during the systematic literature review

Author	Year	Exclusion Reason	Exclusion Sub-reason
Studies excluded at full-text screening, during the SLR update (July 2021)			
Bowers et al	2020	Other	Conference abstract
Casassa et al	2020	Other	Not published in English
Cavalieri et al	2019	Other	Reporting from same data cut as previously included study, no new outcomes reported
Clingan et al	2020	Other	Conference abstract
Clover et al	2020	Population	Not locally advanced/metastatic CSCC
Creighton et al	2018	Intervention	Surgical interventions
Deilhes et al	2019	Intervention	Mixed interventions including surgery
Eglmeier et al	2020	Study design	Case series < 10 pts with locally advanced disease
Gonzalez et al	2019	Intervention	No intervention/intervention not clear
Greco et al	2020	Other	Conference abstract
Harris et al	2020	Other	Conference poster
Hasmat et al	2019	Intervention	No intervention/intervention not clear
Hiura et al	2019	Other	Conference abstract
Ho et al	2020	Other	Conference abstract
Hober et al	2020	Other	Conference abstract
Hughes et al	2020	Other	Conference abstract
Jin et al	2018	Other	Conference abstract

Author	Year	Exclusion Reason	Exclusion Sub-reason
Kim et al	2020	Intervention	No intervention/intervention not clear
Licitra et al	2017	Other	Conference abstract
Lin et al	2021	Other	Study protocol
Lu et al	2015	Duplicate publication	Publication year incorrectly indexed
Lu et al	2015	Duplicate publication	Publication year incorrectly indexed
Migden et al	2019	Other	Conference abstract
Naing et al	2019	Other	Conference abstract
Nct et al	2019	Other	No results posted
Nottage et al	2016	Duplicate publication	-
Owonikoko et al	2018	Other	Conference poster
Papadopoulos et al	2018	Other	Conference abstract
Peyrade et al	2018	Other	Conference abstract
Rabinowits et al	2020	Other	Conference poster
Sayan et al	2020	Population	Resectable
Smile et al	2020	Other	Conference abstract
Tejedor Tejada et al	2021	Other	Conference abstract
Trodello et al	2019	Intervention	Only 5 patients treated without surgery
Vaidya et al	2020	Other	Conference abstract
Vasan et al	2020	Intervention	No intervention/intervention not clear
Zalaudek et al	2019	Study design	Case report letter

Author	Year	Exclusion Reason	Exclusion Sub-reason
*	2019	Other	Conference abstract
Studies excluded at full-text screening, during the initial SLR (May 2019)			
Anasagasti-Angulo et al	2009	Study design	< 10 cases of CSCC patients
Arenas et al	2015	Study design	Case series < 10 pts with locally advanced disease
Assam et al	2016	Study design	Case report
Barnes et al	2010	Population	Mixed population
Barysch et al	2012	Population	Mixed population
Bossi et al	2012	Study design	Case report
Bowles et al	2014	Population	Not CSCC
Brewster et al	2007	Population	Disease-free at randomization
Brunner et al	1985	Study design	Observational study < 10 patients with SCC, and no outcomes of interest
Burgin et al	2017	Population	Newly diagnosed CSCC of head and neck - disease staging is unclear in this conference abstract.
Caccialanza et al	1999	Outcomes	No outcome of interest
Caccialanza et al	1997	Population	Mixed population
Caccialanza et al	2001	Population	Mixed population
Caccialanza et al	2003	Outcomes	No outcome of interest
Caccialanza et al	2009	Study design	< 10 advanced CSCC patients
Campana et al	2014	Outcomes	No outcome of interest
Cartei et al	2000	Population	Mixed population
Carter et al	2013	Study design	< 10 cases of CSCC patients
Caruso et al	1987	Study design	Case report of 1 patient and review of 7 other reported cases

Author	Year	Exclusion Reason	Exclusion Sub-reason
Cassisi et al	1978	Outcomes	No outcome of interest
Chen et al	2007	Population	Patients with local resectable non-advanced lesions amenable to Mohs surgery were included. Results not reported separately.
Cranmer et al	2010	Other	Review
Dean et al	2011	Study design	Tumor excision with or without LN resection/parotidectomy in stage III/IV CSCC
Dormand et al	2010	Study design	Surgery for CSCC in a study with only 6 metastatic patients; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Ducassou et al	2011	Outcomes	Outcomes are not reported separately for the SCC patients who received brachytherapy in the non-adjuvant setting; also, staging (advanced/metastatic status) of the SCC patients is not clear.
Dummer et al	2008	Study design	<10 cases of CSCC patients
Dundar et al	2018	Population	Local disease - No mention of metastasis - all resectable
Ebrahimi et al	2010	Outcomes	No outcome of interest
Engelhardt et al	2011	Study design	Case report
Epstein et al	1981	Other	Letter
Erkan et al	2017	Study design	Surgery for CSCC in a study with only 2 patients with N1 disease and no patients with M1 disease.; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Erlichman et al	2006	Study design	< 10 cases of CSCC patients
Falchook et al	2012	Population	Not CSCC (table 2)
Faustina et al	2004	Study design	< 10 cases of CSCC patients who received RT without surgery.

Author	Year	Exclusion Reason	Exclusion Sub-reason
Fitzpatrick et al	1985	Population	All patients had local disease (regional metastases "developed" after treatment); many pts had surgery. Resectability is not mentioned.
Ganesan et al	2016	Study design	Case report
Gathings et al	2014	Study design	Case report
Geraud et al	2015	Study design	Case report
Glenn et al	2015	Study design	Case report
Gluck et al	2009	Study design	<10 cases of CSCC patients
Gonzalez et al	2019	Population	Local disease - local recurrence, as well as nodal, in-transit, and distant metastases were outcomes of interest; interventions included Mohs, excision, and electrodessication and curettage
Goto et al	2017	Outcomes	No outcome of interest
Groselj et al	2018	Study design	< 10 CSCC pts in each intervention group
Gustaityte-Larsen et al	2013	Study design	Case series <10 pts with locally advanced disease
Guthrie et al	1985	Study design	< 10 CSCC pts in each intervention group
Hamandi et al	2018	Population	Not CSCC (lung transplant patients)
Hausauer et al	2013	Intervention	Intervention is not clear (mix of Mohs surgery, other types of surgery, topical treatment or no treatment)
Heath et al	2013	Study design	Surgery+Erlotinib+RT for CSCC in a study with only 8 patients with at least N1 disease.; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Heffelfinger et al	2013	Population	Invasive (not metastatic) CSCC undergoing microvascular free flaps repair; Abstract of this study was included back on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.

Author	Year	Exclusion Reason	Exclusion Sub-reason
Herman et al	2016	Outcomes	Distant metastais-free survival (DMFS) and cause-specific survival (CSS) (time to death from CSCC or a treatment complication) were reported. ; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Hernandez-Machin et al	2007	Population	Mixed population
Jenni et al	2016	Study design	<10 cases of CSCC patients
Kadakia et al	2016	Study design	Surgery for CSCC in a study where patients with distant metastasis were excluded. Regional lymph node metastasis was not commented on; however, the population seems to have mainly had local disease (only 6 patients had bony invasion); Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Kalaghchi et al	2018	Population	Patients were excluded from the study if their lesions […] metastasized the lymphatics or distant viscera. The patients underwent clinical examination with fully exposed skin and imaging studies as indicated to rule out nodal/visceral metastasis. All pts had either T1-2 N0 lesions (not advanced) or underwent surgical excision (resectable)
Khan et al	1999	Study design	Surgery for CSCC in a study where patients were excluded if they had clinical evidence of lymph node involvement at presentation.; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Kouloulias et al	2001	Population	Mixed population
Kraus et al	1998	Population	Resectable ("All tumors would otherwise have been treated by excision surgery, curettage/electrodesiccation, or cryotherapy").
Kreuter et al	2015	Study design	<10 cases of CSCC patients

Author	Year	Exclusion Reason	Exclusion Sub-reason
Kropp et al	2013	Population	Mohs surgery for a mixed population of BCC and CSCC in a study where all patients were node-negative. It seems that patients generally have local disease since patients with gross PNI were excluded.
Lacouture et al	2013	Population	Melanoma
Lambert et al	1990	Population	Resectable
Landthaler et al	1989	Other	Article is in German
Lassen et al	2016	Population	Mix of solid tumors
Lazarus et al	1980	Study design	Case report
Lewis et al	2012	Population	Mix of resectable and unresectable CSCC; not clear how many of laCSCC patients had resectable disease; too many intervention groups (almost all permutations feasible with gefitinib, surgery and RT have been administered - Figure 1); pts have already had at least SD response to gefinitib
Lin et al	2012	Population	Almost all CSCC pts had local disease (>92% - Table 1) and almost all patients had surgery (96% - Table 1) (resectable laCSCC)
Lu et al	2017	Population	Pts are not specified to be laCSCC or mCSCC (as expected since treatment is PDT)
Ma et al	2016	Study design	< 10 cases of CSCC patients
Manyam et al	2017	Outcomes	No outcome of interest
Manyam et al	2015	Outcomes	61% of patients were lymph-node positive, but results were not reported for them separately. Distant metastatic patients were excluded.; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Martins et al	1999	Outcomes	OS rate is the only outcome of interest (timepoint is unknown); however, CSCC subgroup is a mix of cancers that either directly invaded or metastasized to the parotid gland, and the outcome was not reported for these two groups separately.; Abstract of this study was included back on or after

Author	Year	Exclusion Reason	Exclusion Sub-reason
			January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
McLaughlin et al	2017	Study design	Surgery for CSCC in a study where the outcome is rate of LN metastasis. Baseline N and M status of patients is not clear; however, since the intervention is Mohs surgery, it is safe to assume that all patients had local disease.; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
McNab et al	1997	Study design	<10 cases with CSCC who received RT; the others either received surgery or did not receive treatment at all.
Miller et al	1982	Study design	<10 cases of CSCC patients
Nakamura et al	2013	Study design	<10 cases of CSCC patients
Nasser et al	2014	Study design	Surgery for CSCC in a study where only 4 patients (6%) had LN metastasis with no patient with distant metastasis.; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Nottage et al	2016	Other	Relevant conference abstract - does not provide any additional data compared to corresponding full-text publication (Nottage 2017)
Palmer et al	2018	Population	All pts have already received surgery at the beginning of study, some went on to receive RT and some RT+Cetuximab; over half of the pts have N0 stage [i.e. resectable laCSCC] - Table 1)
Panizza et al	2012	Population	Resectable laCSCC
Peng et al	1347	Population	Mixed population
Peris et al	2006	Study design	<10 cases of CSCC patients
Plopper et al	2004	Outcomes	No outcome of interest

Author	Year	Exclusion Reason	Exclusion Sub-reason
Porceddu et al	2018	Population	RCT randomizing patients who have already undergone resection for laCSCC or regional mCSCC lesions to RT or RT + carboplatin. Results are not reported for the regional mCSCC subgroup, separately. (mixed population)
Porceddu et al	2017	Population	Same trial as S5000: This is basically an RCT randomizing patients who have already undergone resection for laCSCC or regional mCSCC lesions to RT or RT + carboplatin. Results are not reported for the regional mCSCC subgroup, separately. (mixed population) (conference abstract? http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.6008)
Pugliano-Mauro et al	2010	Intervention	Mohs surgery for high-risk CSCC. Metastasis status was not reported; however, it is safe to assume that all patients had local disease.; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Rakkhit et al	2007	Other	Review
Raut et al	2004	Study design	< 10 pts with CSCC (Table)
Reigneau et al	2015	Outcomes	No outcome of interest
Roth et al	2019	Population	Not advanced - Superficial RT is being compared to Mohs surgery in various sections of the article. No mention of advanced, unresectable, or metastatic disease in the publication.
Salah et al	2017	Population	Over 38% of population had cancer of upper or lower lip. CSCC patients who were treated with RT alone are retrospectively reviewed. Staging is not clear in this conference poster.
Salido-Vallejo et al	2016	Study design	Surgery for CSCC in a study where none of the patients had LN or distant metastasis (all stage I or II disease).; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Sherman et al	1993	Study design	Altogether (case report + review of previous case reports), <10 cases with CSCC received RT without surgery.

Author	Year	Exclusion Reason	Exclusion Sub-reason
Shibao et al	2017	Other	Letter
Shiffman et al	1975	Population	“Invasion of the cartilage at the time of diagnosis had occurred in 11 lesions. At this time none showed any evidence of skin, lymph-node or distant metastases.” Therefore, all patients had local/locally advanced disease, and all (except 2) also underwent surgery → Resectable laCSCC.
Shimm et al	1991	Population	Mix of local and locally advanced disease half of which were eligible for surgery. Also, no outcome of interest.
Shin et al	2002	Population	Mixed population
Sibar et al	2016	Outcomes	No outcome of interest
Somanchi et al	2008	Outcomes	No outcome of interest
Strassen et al	2017	Study design	Surgery for CSCC: Pt characteristics table 1 has errors with respect to n and p of patients who had at least an N1 status at recurrence. Of note, only five patients (8%) had M1 status at recurrence.; Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Subramaniam et al	2017	Outcomes	No outcome of interest
Sweeny et al	2012	Population	Mix of all stages - All underwent resection - KM curves for regional mCSCC separated for EGFR+ and EGFR- are available
Tang et al	2013	Study design	RT (in the form of sterotactic radiosurgery) ± local excision for locally advanced disease. Changed from "Excluded by Intervention" to current decision on or after January 9, 2018 because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Tanvetyanon et al	2015	Population	Mixed population
Tavin et al	1996	Outcomes	No outcome of interest
Teli et al	2009	Study design	Local excision + RT to primary site and regional nodes. Changed from "Excluded by Intervention" to current decision on or after January 9, 2018

Author	Year	Exclusion Reason	Exclusion Sub-reason
			because LN dissection/parotidectomy in regional/distant metastatic patients are now of interest.
Templeton et al	1986	Study design	Case report
Tsao et al	2002	Study design	<10 cases of CSCC at stages T3 or T4 (table 1)
van Hezewijk et al	2010	Outcomes	No outcome of interest
Veness et al	2006	Outcomes	No outcome of interest
Viros et al	2013	Population	Animals
Wan et al	1991	Outcomes	No outcome of interest
Warren et al	2016	Population	All patients are under T3
Westers-Attema et al	2015	Study design	Case report
Wilson et al	1990	Study design	<10 cases of CSCC patients
Zhu et al	2015	Intervention	Surgery/radiotherapy

Notes: * no author was reported for the citation, the title of the study was “Phase ii trial of pembrolizumab (mk-3475) in metastatic cutaneous squamous cell carcinoma: An updated analysis” and was identified through the CCRT database.

EMPOWER-CSCC 1 trial

A2. Were there any differences in any clinical outcomes between the weight-based dose and fixed-dose groups within EMPOWER-CSCC 1 at the July 2021 data cut? If so, please describe these.

Sanofi response:

Formal analyses of these subgroups for the July 2021 DCO are not currently available, the analyses have been requested and will be shared with NICE/ERG upon receipt.

However, no meaningful divergence from previously reported efficacy in these groups is expected because all patients completed treatment more than ***one*** year prior to the data cut. ***Specifically***, the date of last dose of study drug for any patient was 13 Feb 2019 for Group 1 (weight-based), 23 Jan 2020 for Group 2 (weight-based), and 27 Feb 2020 for Group 3 (fixed dose)***.*** Visual inspection of patient level efficacy results in the Analysis Data Model (A***D***aM) data set does not suggest any emergence of notable differences from prior efficacy results. To supplement the efficacy analysis, results from a previous data cut (October 2020) have been provided below. Table 2 shows the objective response rate efficacy data by cohort while Figure 1and Figure 2 capture PFS and OS, respectively. While no statistical tests between cohorts have been conducted, few numerical differences in efficacy are seen between cohorts across all endpoints, specifically between cohorts 1 and 3 which show the weight-based dose results for mCSCC patients and fixed-dose results for mCSCC patients.

Table 2: Objective Response Rates of EMPOWER-CSCC 1 by Patient Group (Independent Central Review) - OCTOBER 2020 DCO

	Group 1 mCSCC, cemiplimab 3 mg/kg Q2W (n = 59)	Group 2 laCSCC, cemiplimab 3 mg/kg Q2W (n = 78)	Group 3 mCSCC, cemiplimab 350 mg Q3W (n = 56)	Total (n = 193)
ORR, % (95% CI)	50.8 (37.5-64.1)	44.9 (33.6-56.6)	46.4 (33.0-60.3)	47.2 (39.9-54.4)
PR, n (%)	18 (30.5)	25 (32.1)	15 (26.8)	58 (30.1)
CR, n (%)	12 (20.3)	10 (12.8)	11 (19.6)	33 (17.1)
Stable disease, n (%)	9 (15.3)	27 (34.6)	8 (14.3)	44 (22.8)
Non-CR/non-PD[a], n (%)	3 (5.1)	0	2 (3.6)	5 (2.6)
Progressive disease, n (%)	10 (16.9)	10 (12.8)	14 (25.0)	34 (17.6)
Not evaluable[b], n (%)	7 (11.9)	6 (7.7)	6 (10.7)	19 (9.8)
Disease control rate[c], % (95% CI)	42 (71.2)	62 (79.5)	36 (64.3)	140 (72.5)
	(57.9-82.2)	(68.8-87.8)	(50.4-76.6)	(65.7-78.7)
Durable disease control rated, % (95% CI)	36 (61.0)	49 (62.8)	32 (57.1)	117 (60.6)
	(47.4-73.5)	(51.1-73.5)	(43.2-70.3)	(53.3-67.6)
Median observed time to response, months (IQR)	1.9 (1.8-2.0)	2.1 (1.9-3.8)	2.1 (2.1-4.2)	2.1 (1.9-3.7)

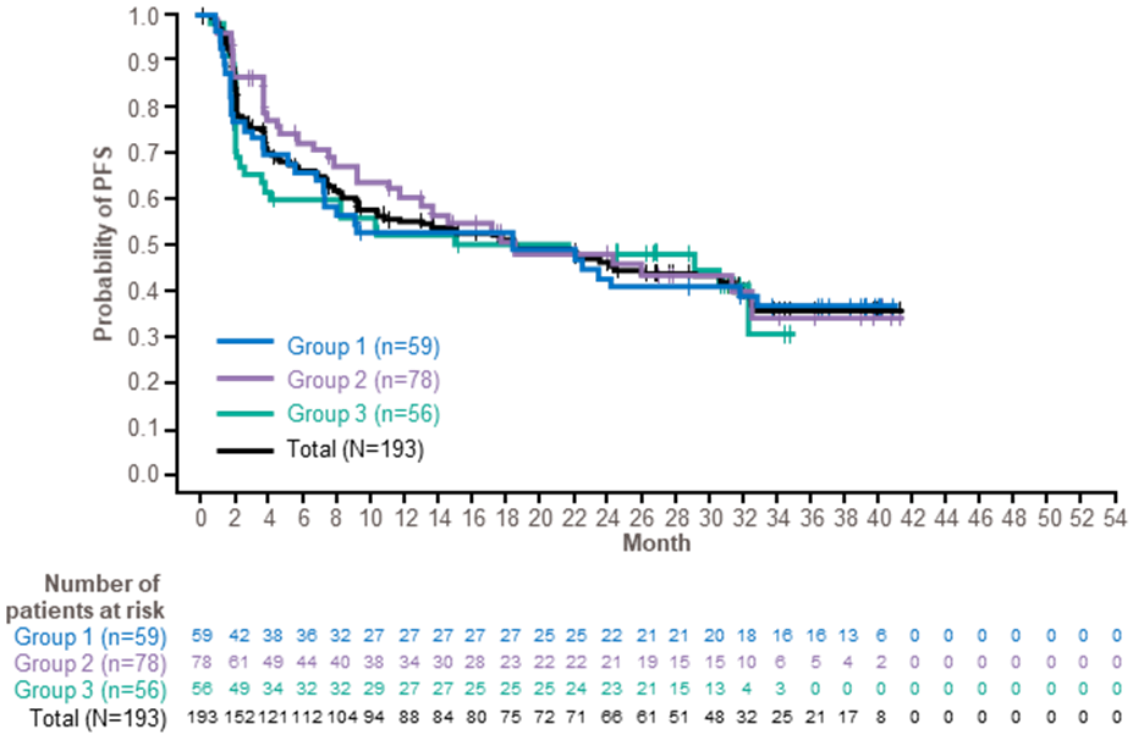
CI = confidence interval; CR = complete response; IQR = interquartile range; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; ORR = objective response rate; PD = progressive disease; PR = partial response; Q2W = every 2 weeks; Q3W = every 3 weeks.

[a] Non-CR/Non-PD is for patients with non-measurable disease only.
[b] Not evaluable response includes missing and unknown tumour response.
[c] Disease control rate is CR + PR + stable disease + non-CR/non-PD.
[d] Durable disease control is defined as the proportion of patients without progressive disease for at least 105 days.
Note: Data cut-off date: 11 October 2019.

Median duration of follow-up: Group 1: 18.5 months; Group 2: 15.5 months; Group 3: 17.3 months; and total (all 3 groups): 15.7 months.

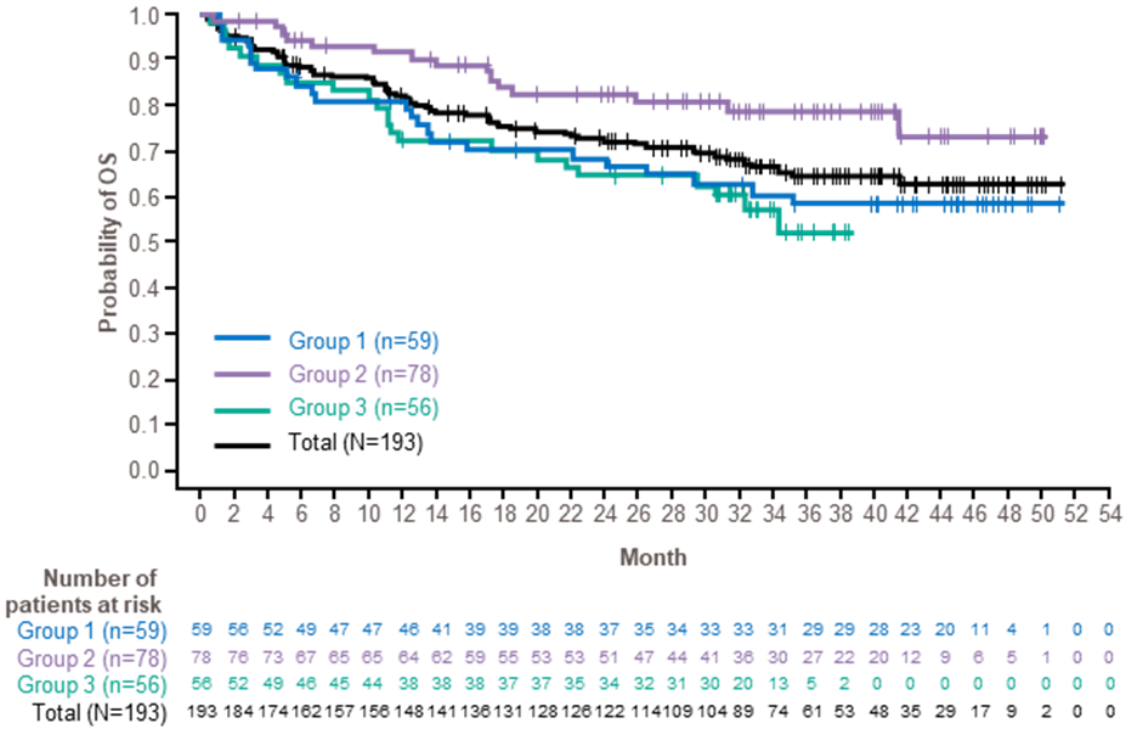
Source: Rischin et al. 2021[1]

Figure 1: EMPOWER-CSCC 1: Kaplan-Meier Curve of Progression-Free Survival by Independent Central Review (Full Analysis Set) - OCTOBER 2020 DCO



Number of patients at risk																											
Group 1 (n=59)	59	42	38	36	32	27	27	27	27	27	25	25	22	21	21	20	18	16	16	13	6	0	0	0	0	0	0
Group 2 (n=78)	78	61	49	44	40	38	34	30	28	23	22	22	21	19	15	15	10	6	5	4	2	0	0	0	0	0	0
Group 3 (n=56)	56	49	34	32	32	29	27	27	25	25	25	24	23	21	15	13	4	3	0	0	0	0	0	0	0	0	0
Total (N=193)	193	152	121	112	104	94	88	84	80	75	72	71	66	61	51	48	32	25	21	17	8	0	0	0	0	0	0

Figure 2: EMPOWER-CSCC 1: Kaplan-Meier Curve of Overall Survival by Independent Central Review (Full Analysis Set) - OCTOBER 2020 DCO



Number of patients at risk																											
Group 1 (n=59)	59	56	52	49	47	47	46	41	39	39	38	38	37	35	34	33	33	31	29	29	28	23	20	11	4	1	0	0
Group 2 (n=78)	78	76	73	67	65	65	64	62	59	55	53	53	51	47	44	41	36	30	27	22	20	12	9	6	5	1	0	0
Group 3 (n=56)	56	52	49	46	45	44	38	38	38	37	37	35	34	32	31	30	20	13	5	2	0	0	0	0	0	0	0	0
Total (N=193)	193	184	174	162	157	156	148	141	136	131	128	126	122	114	109	104	89	74	61	53	48	35	29	17	9	2	0	0

SACT cohort

A3. PRIORITY QUESTION. CS section A.6.5 gives only a summary of the SACT cohort dataset. Please provide the full cemiplimab dataset from SACT as supplied by NHS England Digital.

Sanofi response:

The SACT report produced by the NHS England digital teams titled "TA592_Cemiplimab_final_report_draft_CONFIDENTIAL_v4" was uploaded to NICEdocs following the Clarification question meeting and included within the supplementary materials for this response document. This is all the information received by Sanofi following review of the SACT data collection period, no patients level data was received.

Eligibility criteria for use of cemiplimab within the Cancer Drugs Fund (CDF) were aligned to the recommendations published for cemiplimab up on entry (TA592).

A4. PRIORITY QUESTION. Please explain the eligibility criteria that NHS Digital England used to select cemiplimab-eligible/treated patients from the SACT database.

Sanofi response:

See response to A3

A5. PRIORITY QUESTION. Did the company apply any further eligibility criteria to select patients from the dataset supplied by NHS Digital England? If so, please explain these.

Sanofi response:

See response to A3

A6. PRIORITY QUESTION. Were there any patients in the SACT dataset who did not receive cemiplimab as intended? If so, please describe them.

Sanofi response:

As mentioned above, patient level data was not made available to the Company for patients treated through the CDF. Our understanding following discussions with clinicians is that at the start of the CoVid-19 pandemic there was disruption to the provision of service, resulting in some patients not receiving cemiplimab as intended. Clinical experts noted a drop in referrals during the early period of the pandemic with patients subsequently presenting with more advanced disease, which may have had an impact on assessment, treatment options and outcomes. Some clinical experts also reported that COVID-19 led to extended dosing intervals and missed doses of cemiplimab.

UK chart review

A7. PRIORITY QUESTION. Please indicate which data were changed following the audit process and why.

Sanofi response:

A copies of the Case report form (CRF) from the original (MDA_cSCC_Pt_CRF__laCSCC MAIN STUDY_16JAN2018 and MDA_CSCC_Pt_CRF__mCSCC MAIN STUDY_24APR2018) and audit (UK CSCC PT FOLLOW-UP CRF 1 OCT 2020 FINAL) are included in the supplementary material for this response. For additional information on how these audited data were used to enrich the dataset, please see Clarification Question A8. A supplemental CRF was developed based on input from a UK physician. Additional data points around excisional biopsies, surgeries, radiotherapy, and systemic treatments both before and after their advanced CSCC diagnosis. The detailed data fields are shown below, pre-populated data fields in section 1 and 2 were confirmed / modified by the SIs.

A8. CS section A.6.2.1 states that the audited data were integrated into the original data set to "enrich" the profiles of audited patients. What does "enrich" mean? Did these patients have more data than the non-audited patients, or data that were regarded as being more accurate? If so, please provide the details.

Sanofi response:

The term enrich was used to describe records where additional information was collected as part of the audit (as outlined in the response to Clarification question A7). Where data points changed between the original chart review and the audit, data from the audit superseded that from the original chart review as it was anticipated that data points collected in the audit were more accurate than those collected during the original chart review. Figure 4 presents swimmer plot from audited cohort and their original chart review swimmer plots.

A9. PRIORITY QUESTION. CS section A15.5 (page 119) states "locally advanced patients were excluded from the retrospective chart review if they

had received surgery, RT or topical chemotherapy for the target lesion during study period or had confirmatory evidence of metastases".

(a) This statement appears ambiguous because it is not explicit whether the surgery, RT or topical therapy mentioned here for laCSCC patients was for curative or non-curative intent. But as these patients were diagnosed with laCSCC why would they not be eligible for cemiplimab therapy? Please explain why they were excluded and how many patients this decision applies to.

(b) Those patients with laCSCC who had evidence of metastasis would still be classified as having advanced CSCC so why would they not be eligible for cemiplimab therapy? Please explain why they were excluded and how many patients this decision applies to.

Sanofi response:

A9(a):

Cemiplimab as monotherapy is indicated for the treatment of adult patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation.[2] To be included in Group 2 (unresectable laCSCC) of EMPOWER CSCC-1, surgery must have been deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon. Patients must also be deemed as not appropriate for radiation therapy. Criteria further specifying reasons for non-eligibility for surgery or radiation for Group 2 are provided in further detail within the study protocol for R2810-ONC-1540 (EMPOWER-CSCC 1). [3]

The chart review study protocol ("CSCC Chart Review Study Protocol FINAL 17DEC2017_rev 04Jan2018 (with Italy)") is included within the supplementary material to this response Full inclusion and exclusion criteria from the chart review study are outlined in Section 5.2.2 and Section 5.2.3. The intent of these criteria is to model a cohort most similar to the EMPOWER CSCC-1 trial population.

As recurrent disease makes up a large proportion of those not eligible for curative surgery or radiotherapy, inclusion criteria 5a specifies patients cannot receive further surgery / RT in the same location. In addition, either criteria 5b or 5c stipulates that these patients received non-curative intent systemic treatments or no active therapy

(BSC). Given that detailed chart notes on eligibility for curative surgery / RT are not readily available within the charts, these criteria taken together attempt to mimic the criteria applied within EMPOWER-CSCC1. Exclusion criteria 5 and 6 related to surgery and RT make clear that minor or non-target lesion procedures with palliative intent would not warrant exclusion from the chart review study. Exclusion criteria 8 restricts topical therapy as these agents are only used for early-stage disease, thus warranting exclusion from the study.

A9 (b):

Patients with evidence of metastasis would have been excluded from the laCSCC cohort as these patients would no longer qualify as having laCSCC. Instead, these patients would be assigned to the mCSCC cohort per the chart review inclusion and exclusion criteria. Please see exclusion criteria 7 above.

A10. PRIORITY QUESTION. CS section A.15.6 (page 122) states "*many* patient records consisted of data with long periods of time with no event or no visit data", and Appendix A1 in the UK chart review report (reference 12) (page 46) states "the audit "identified *numerous* laCSCC patients who received excision biopsies both during and following systemic therapy". Please clarify the number of patients that "many" and "numerous" refer to in the statements above.

Sanofi response:

Figure 3 presents a swimmer plot of patient histories from the original chart review cohort (n=106). As demonstrated by the swimmer plot, many patient records consisted of data with long periods of time with no events or visit data. For example, the first laCSCC patient presented in the swimmer plots (50041_4) stops treatment at ~11 months and then the next visit logged is the patient's last visit at ~78 months. In total, [redacted] patients in the original chart review had follow-up gaps of more than [redacted] months where no visits were confirmed to have occurred.

Figure 4 presents swimmer plots of the patients who were included in the audit (n=52), reporting patient histories both in the original chart review data set (left) and following the audit. There [redacted]

[redacted]

Figure 3: Swimmer plot of patient histories for UK cohort (original chart review); all patients including untreated patients (n=106)

Figure 4: Swimmer plots of audited patients in original (left) and audit (right) data sets (n=[redacted])

A11. PRIORITY QUESTION. Section 3.1.2 of the UK chart review report does not describe how data were extracted from the chart review records. How many reviewers extracted the data? Were any error checks conducted?

Sanofi response:

The Sponsor contracted study execution to a third party vendor, Medical Data Analytics (now RTI Health Solutions). The vendor reached out to sites directly for recruitment, start-up, data collection, and data validation. The Sponsor had no direct contact with sites or de-identified patient data. Senior investigators (SIs) were identified at each site, these SIs had autonomy in determining the number of reviewers, and how the data were collected and validated. A detailed description of the vendor data validation process is described below.

The data collection process is described in the chart review protocol as follows:

- The SIs and/or their assigned staff will be responsible for patient chart identification, qualification and selection, data abstraction and completion of the patient Clinical record form (CRF). Clinical data will be sourced from patient medical records (electronic and/or hard copy/paper).

- SIs and/or site staff will be instructed to assign a unique identifier for each patient enrolled in the study for the purpose of follow up. Patient data will be de-identified and will be reported in aggregate.

- Electronic CRFs will be programmed to be available online via encrypted, password protected access. Alternatively, sites will be allowed to submit paper-based CRFs via express mail. The data entry will be checked for consistency and accuracy and any discrepancy will be reconciled using the paper-based CRF.

Further, monitoring and site data quality control for the chart review were described as follows:

- "Data management quality control will be based on a Targeted Abstraction Process (TAP). Physician involvement is an important and distinguishing feature of TAP. Physicians are recruited for study participation with the understanding that they will operate as SIs with responsibility for patient selection, chart data abstraction and data validation/resolution. This responsibility and direct involvement by physicians enhances data quality through minimization of inaccurate, missing, or incomplete data and data misinterpretation that often occur in such studies. Quality control measures include:

    1. Data validation, resubmission of data for key data points such as date of diagnosis, date of therapy initiation, hospitalizations, patient status (alive or deceased) of at least 30% of completed CRFs will be conducted
    2. Range checks, CRF scanning for data inconsistency, data entry, reporting of the proportion of missing data at the item and individual level, examination of frequencies and distributions, as well as the generation of descriptive statistics. This will be conducted for 30% of the completed CRFs to be implemented online
    3. Internet-based CRF will be programmed to provide immediate error alerts upon entry of out of range values
    4. Internet-based CRF will also promote data completeness by not allowing physicians to advance to subsequent section until required fields are entered
- Data cleaning, data validations and database lock will be conducted prior to the statistical analyses. Frequency distributions of all parameters will be performed as a final check to identify any out of range, illogical or erroneous values prior to lock.

All work will be subject to quality control and documentation procedures, to make certain the report is accurate and thorough, and the analyses can be reproduced."

A12. PRIORITY QUESTION. CS section A.15.8 (page 128) states "The data quality for prior RT, specifically the dates of administration, was considered too poor to be used in any analysis and this variable was also excluded from the analysis". Please clarify what the problems with the data for prior RT were and how many patient records these affected.

Sanofi response:

In the chart review data sets (both original and audit), there were two variables for administration of radiotherapy (RT). The PURP variable (variable from MDA that identified palliative RT) was available in the original dataset (n=106) and indicated that [redacted] patients received palliative RT; however, dates of administration were not recorded for this variable. The second variable, RAD_REASON, was included in the audited data set only [redacted]. The variable reported dates associated with RT administration, which flagged that [redacted]

Note clinical experts indicated the reported rates of prior RT were lower than would be expected in the target population. Due to incomplete reporting of dates and reason for RT administration in both the original and audited datasets, RT was not evaluated in the indirect comparison.

Indirect treatment comparisons

A13. CS section A.7.1 states that "the covariates (prognostic factors) were identified through a targeted literature review and validated by clinical expert opinion", citing reference 8 (Keeping et al.). Please explain why a targeted search, and not a systematic search, was carried out to identify the covariates (prognostic factors).

Sanofi response:

The search conducted to identify the relevant prognostic factors in Keeping et al.[4] is the same search as described in **Section B.2.9.1.1.** of the Company submission for TA592. The same review is relevant to the current submission. For clarity, we have

included the text from the original submission below, which described the systematic approach to the targeted review. Although not a formal systematic review, structured searches were conducted and results validated by clinical experts; therefore it was deemed low risk that any potentially relevant evidence would have been missed.

- “In order to mitigate this issue as far as possible, a systematic approach was developed to identify relevant prognostic factors. First, a targeted search was carried out in PubMed using the search query:
    - (("squamous cell carcinoma"[Title] AND ("skin"[Title] OR "cutaneous")[Title]) AND prognos*[Title/Abstract])
- Prognostic factors identified from this search were then validated by consulting clinicians with experience treating advanced CSCC patients.
- Detailed results of the targeted search are presented in Appendix D.1.3.3 (Company submission for TA592). The most important prognostic factors identified from the literature included immune status, disease stage, age and tumour differentiation grade. A summary of identified prognostic factors is presented in Table 8 of Appendix D.1.3.3 (Company submission for TA592).
- Secondly, given that EMPOWER-CSCC 1 represents the largest study in this population, a descriptive statistical analysis (that is a univariate Cox regression) was conducted using data from the cemiplimab trial to investigate trial outcomes for subgroups if this data were available. The aim of this was to determine whether or not the identified prognostic factors actually influences the results within those strata in the cemiplimab trials, and whether any additional factors showed evidence of having prognostic value. Of note, this descriptive analysis was limited by the small sample size of the cemiplimab trials and therefore, any index of statistical significance (for example p values) were not considered relevant to the exercise.”

A14. The cited reference by Keeping et al. does not report any results of the targeted search, any information on how studies were selected, any models for exploring prognostic factors, or any validation by expert opinion. Please provide this information.

Sanofi response:

The studies identified from the targeted search and the validation of prognostic factor with clinical experts are described in response to Clarification questions (A7 and A8) from the Company submission for TA592.

The targeted search identified 28 studies that reported on factors that had prognostic value on either OS or PFS. The citations are as follows:

1. Bachar G, Mizrachi A, Rabinovics N, et al. Prognostic factors in metastatic cutaneous squamous cell carcinoma of the head and neck. *Ear Nose Throat J.* 2016;95(10-11):E32-E36.
2. Brinkman JN, Hajder E, van der Holt B, Den Bakker MA, Hovius SE, Mureau MA. The Effect of Differentiation Grade of Cutaneous Squamous Cell Carcinoma on Excision Margins, Local Recurrence, Metastasis, and Patient Survival: A Retrospective Follow-Up Study. *Ann Plast Surg.* 2015;75(3):323-326. doi: 310.1097/SAP.0000000000000110.
3. Czerwonka L, De Santis RJ, Horowitz G, et al. Staging cutaneous squamous cell carcinoma metastases to the parotid gland. *Laryngoscope.* 2017;127(9):2063-2069. doi: 2010.1002/lary.26544. Epub 22017 Mar 26514.
4. Estall V, Allen A, Webb A, Bressel M, McCormack C, Spillane J. Outcomes following management of squamous cell carcinoma of the scalp: A retrospective series of 235 patients treated at the Peter MacCallum Cancer Centre. *Australas J Dermatol.* 2017;58(4):e207-e215. doi: 210.1111/ajd.12520. Epub 12016 Jun 12510.
5. Goh RY, Bova R, Fogarty GB. Cutaneous squamous cell carcinoma metastatic to parotid - analysis of prognostic factors and treatment outcome. *World J Surg Oncol.* 2012;10:117.(doi):10.1186/1477-7819-1110-1117.
6. Hirshoren N, Danne J, Dixon BJ, et al. Prognostic markers in metastatic cutaneous squamous cell carcinoma of the head and neck. *Head Neck.* 2017;39(4):772-778. doi: 710.1002/hed.24683. Epub 22017 Feb 24615.
7. McLean T, Brunner M, Ebrahimi A, et al. Concurrent primary and metastatic cutaneous head and neck squamous cell carcinoma: Analysis of prognostic factors. *Head Neck.* 2013;35(8):1144-1148. doi: 1110.1002/hed.23102. Epub 22012 Aug 23121.
8. Mizrachi A, Hadar T, Rabinovics N, et al. Prognostic significance of nodal ratio in cutaneous squamous cell carcinoma of the head and neck. *Eur Arch Otorhinolaryngol.* 2013;270(2):647-653. doi: 610.1007/s00405-00012-02050-00403. Epub 02012 May 00413.
9. Sweeny L, Zimmerman T, Carroll WR, Schmalbach CE, Day KE, Rosenthal EL. Head and neck cutaneous squamous cell carcinoma requiring parotidectomy: prognostic indicators and treatment selection. *Otolaryngol Head Neck Surg.* 2014;150(4):610-617. doi: 610.1177/0194599814520686. Epub 0194599814522014 Jan 0194599814520628.
10. Tseros EA, Gebski V, Morgan GJ, Veness MJ. Prognostic Significance of Lymph Node Ratio in Metastatic Cutaneous Squamous Cell Carcinoma of the Head and Neck. *Ann*

Surg Oncol. 2016;23(5):1693-1698. doi: 1610.1245/s10434-10015-15070-10436. Epub 12016 Jan 10419.

11. Vasan K, Low TH, Gupta R, et al. Lymph node ratio as a prognostic factor in metastatic cutaneous head and neck squamous cell carcinoma. *Head & neck.* 2018;23(10):25066.
12. McDowell LJ, Tan TJ, Bressel M, et al. Outcomes of cutaneous squamous cell carcinoma of the head and neck with parotid metastases. *Journal of Medical Imaging and Radiation Oncology.* 2016.
13. McDowell LJ, Young RJ, Johnston ML, et al. p16-positive lymph node metastases from cutaneous head and neck squamous cell carcinoma: No association with high-risk human papillomavirus or prognosis and implications for the workup of the unknown primary. *Cancer.* 2016;122(8):1201-1208. doi: 1210.1002/cncr.29901. Epub 22016 Feb 29916.
14. Manyam BV, Garsa AA, Chin RI, et al. A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck. *Cancer.* 2017;123(11):2054-2060. doi: 2010.1002/cncr.30601. Epub 32017 Feb 30607.
15. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. *JAMA Dermatol.* 2013;149(5):541-547. doi: 510.1001/jamadermatol.2013.2139.
16. Kelder W, Ebrahimi A, Forest VI, Gao K, Murali R, Clark JR. Cutaneous head and neck squamous cell carcinoma with regional metastases: the prognostic importance of soft tissue metastases and extranodal spread. *Ann Surg Oncol.* 2012;19(1):274-279. doi: 210.1245/s10434-10011-11986-10437. Epub 12011 Aug 10439.
17. Gonzalez-Guerrero M, Martinez-Camblor P, Vivanco B, et al. The adverse prognostic effect of tumor budding on the evolution of cutaneous head and neck squamous cell carcinoma. *J Am Acad Dermatol.* 2017;76(6):1139-1145. doi: 1110.1016/j.jaad.2017.1101.1015. Epub 2017 Mar 1114.
18. Forest VI, Clark JJ, Veness MJ, Milross C. N1S3: A revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases - Results of 2 Australian cancer centers. *Cancer.* 2010;116(5):1298-1304.
19. Ch'ng S, Maitra A, Allison RS, et al. Parotid and cervical nodal status predict prognosis for patients with head and neck metastatic cutaneous squamous cell carcinoma. *J Surg Oncol.* 2008;98(2):101-105. doi: 110.1002/jso.21092.
20. Shao A, Wong DKC, McIvor NP, et al. Parotid metastatic disease from cutaneous squamous cell carcinoma: Prognostic role of facial nerve sacrifice, lateral temporal bone resection, immune status and P-stage. *Head and Neck.* 2014;36(4):545-550.
21. Kosec A, Svetina L, Luksic I. Significance of clinical stage, extent of surgery and outcome in cutaneous squamous cell carcinoma of the head and neck. *International Journal of Oral and Maxillofacial Surgery.* 2013;42(1):82-88.
22. Ch'ng S, Maitra A, Lea R, Brasch H, Tan ST. Parotid metastasis--an independent prognostic factor for head and neck cutaneous squamous cell carcinoma. *J Plast*

Reconstr Aesthet Surg. 2006;59(12):1288-1293. doi: 1210.1016/j.bjps.2006.1203.1043. Epub 2006 Jun 1285.

23. Hinerman RW, Indelicato DJ, Amdur RJ, et al. Cutaneous squamous cell carcinoma Metastatic to parotid-area lymph nodes. *Laryngoscope.* 2008;118(11):1989-1996.
24. Oddone N, Morgan GJ, Palme CE, et al. Metastatic cutaneous squamous cell carcinoma of the head and neck: the Immunosuppression, Treatment, Extranodal spread, and Margin status (ITEM) prognostic score to predict outcome and the need to improve survival. *Cancer.* 2009;115(9):1883-1891. doi: 1810.1002/cncr.24208.
25. Cheng J, Yan S. Prognostic variables in high-risk cutaneous squamous cell carcinoma: a review. *J Cutan Pathol.* 2016;43(11):994-1004. doi: 1010.1111/cup.12766. Epub 12016 Aug 12712.
26. Kraus DH, Carew JF, Horrison LB. Regional lymph node metastasis from cutaneous squamous cell carcinoma. Archives of Otolaryngology - Head and Neck Surgery. 1998;124(5):582-587.
27. Li L, Tian Y, Shi C, Zhang H, Zhou Z. Over-Expression of CD200 Predicts Poor Prognosis in Cutaneous Squamous Cell Carcinoma. Med Sci Monit. 2016;22:1079-1084.
28. Carter JB, Johnson MM, Chua TL, Karia PS, Schmults CD. Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: an 11-year cohort study. JAMA Dermatol. 2013;149(1):35-41. doi: 10.1001/jamadermatol.2013.1746.

Prognostic factors were validated by oncologists and dermatologists participating in the expert elicitation exercise. The design and setting of the interviews have been explained in more detail in Appendix M of the Company submission for TA592. The 11 experts participating in the interviews were presented with the list of identified prognostic factors and were asked “Do you agree with the prognostic factors identified for the target population?” and “Are there any other prognostic factors that are missing that you think are important?”. A summary of the experts’ opinions on the list of identified prognostic factors is presented in Table 5. Overall, the experts generally agreed with the list of identified prognostic factors. The only additional prognostic factors suggested by expert 1 were ‘duration of response’ and ‘comorbidities’. These were not reported in Jarkowski et al., 2016 therefore were not included in the comparisons to aggregate data. In the chart review, no patients had prior therapy therefore duration of response wasn’t relevant and data on comorbidities was sparsely collected.

Table 3: Summary of the experts' opinion of the list of identified prognostic factors

Experts	Do you agree with the prognostic factors identified for the target population?	Are there any other prognostic factors that are missing that you think are important?
Expert 1	[redacted]	[redacted]
Expert 2	[redacted]	[redacted]
Expert 3	[redacted]	-
Expert 4	[redacted]	[redacted]
Expert 5	[redacted]	[redacted]
Expert 6	[redacted]	[redacted]
Expert 7	[redacted]	[redacted]
Expert 8	[redacted]	[redacted]
Expert 9	[redacted]	[redacted]
Expert 10	[redacted]	[redacted]
Expert 11	[redacted]	[redacted]

A15. Section 3.2.3 of the UK chart review report (reference 12) states "the prognostic factors were those reported as statistically significant in at least one study identified the targeted review". Please explain (i) which statistical

investigations were made to identify prognostic factors, (ii) which statistical tests were used, and (iii) what "statistically significant" means here.

Sanofi response:

Table 4 presents a summary of the patient and disease characteristics investigated across the prognostic studies, and catalogues which factors were evaluated within the study as potentially prognostic and which were a statistically significant prognostic factor in either univariate or multivariate analyses of OS and/or PFS. Note if a study provided details on both univariate and multivariate analysis, only those factors resulting in statistically significant differences in multivariate analysis are reported in the table. Further, none of the studies addressed potential multicollinearity and interaction among the investigated prognostic factors. No statistical test were conducted using the studies, selection was based on review of the studies only.

Table 4: Summary of the patient/tumor characteristics investigated across the prognostic studies

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
Bachar 2016	Prognostic factors in metastatic cutaneous squamous cell carcinoma of the head and neck	Age	Age	Tumor grade (for disease-free survival)	Tumor grade (for disease-free survival)
Brinkman 2015	The effect of differentiation grade of cutaneous squamous cell carcinoma on excision margins, local recurrence, metastasis, and patient survival: A retrospective follow-up study	Tumor grade	Tumor grade	--	--
Carter 2013	Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: An 11-year cohort study	Age, gender, nerve caliber, tumor diameter <2cm, tumor grade, depth of invasion (beyond subcutaneous fat), number of nerves involved, vascular/lymphatic invasion	Age, tumor diameter <2cm, vascular or lymphatic invasion, depth of invasion (dermis/subcutaneous fat vs. invasion beyond subcutaneous fat)	--	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
Cheng and Yan, 2016	Prognostic variables in high-risk cutaneous squamous cell carcinoma: A review	Scalp or neck (poorer 5-year OS rate) vs. ear or lip; tumor size >2cm; higher expression level for p300 (poorer OS)	Scalp or neck (poorer 5-year OS rate) vs. ear or lip; tumor size >2cm; higher expression level for p300 (poorer OS)	--	--
Ch'ng 2008	Parotid and cervical nodal status predict prognosis for patients with head and neck metastatic cutaneous squamous cell carcinoma	P staging, N stage, extracapsular spread, vascular invasion, perineural invasion, immunosuppression	Positive status for involvement of the parotid gland or cervical lymph nodes, immunosuppression	--	--
Ch'ng 2006	Parotid metastasis--an independent prognostic factor for head and neck cutaneous squamous cell carcinoma	P stage (presence of parotid disease), N stage (presence of neck disease), immunosuppression, extracapsular spread, perineural and vascular invasion.	P stage (presence of parotid disease), N stage (presence of neck disease), immunosuppression	--	--
Czerwonka 2017	Staging cutaneous squamous cell carcinoma metastases to the parotid gland	TNM staging	TNM staging	--	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
Estall 2017	Outcomes following management of squamous cell carcinoma of the scalp: A retrospective series of 235 patients treated at the Peter MacCallum cancer centre	Immunosuppression	Immunosuppression	Immunosuppression	Immunosuppression
Forest 2010	N1s3: A revised staging system for head and neck cutaneous squamous cell carcinoma with lymph node metastases: Results of 2 australian cancer centers	N1S3 staging system	N1S3 staging system	--	--
Goh 2012	Cutaneous squamous cell carcinoma metastatic to parotid - analysis of prognostic factors and treatment outcome	Immunosuppression, perineural invasion, extracapsular extension, tumor grade, number of positive nodes	--	Immune suppression, perineural invasion, extracapsular extension, degree of tumor differentiation (grade), number of positive nodes	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
Gonzalez-Guerrero 2017	The adverse prognostic effect of tumor budding on the evolution of cutaneous head and neck squamous cell carcinoma	Tumor budding	--	--	--
Hinerman 2008	Cutaneous squamous cell carcinoma metastatic to parotid-area lymph nodes	--	--	Tumor grade, perineural invasion, P stage, N stage, extracapsular spread (all for disease-free survival)	--
Hirshoren 2017	Prognostic markers in metastatic cutaneous squamous cell carcinoma of the head and neck	Age, immunosuppression, lymph node ratio (number of positive lymph nodes divided by the total number of nodes)	Age, immunosuppression, lymph node ratio (number of positive lymph nodes divided by the total number of nodes)	--	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
Kelder 2012	Cutaneous head and neck squamous cell carcinoma with regional metastases: The prognostic importance of soft tissue metastases and extranodal spread	Age, lesion size, number of nodes, soft tissue metastasis, extranodal spread	Age, soft tissue metastasis, extranodal spread	Age, lesion size, number of nodes, soft tissue metastasis, extranodal spread (all for disease-free survival)	Soft tissue metastasis, extranodal spread (for disease-free survival)
Kosec 2013	Significance of clinical stage, extent of surgery and outcome in cutaneous squamous cell carcinoma of the head and neck	P staging, N staging, TNM staging (presence of metastasis), tumor size, perineural invasion in regional mCSCC	P staging, N staging, TNM staging (presence of metastasis), perineural invasion in regional mCSCC	--	--
Kraus 1998	Regional lymph node metastasis from cutaneous squamous cell carcinoma	--	--	Tumor grade and N stage (for disease-free survival)	N stage (for disease-free survival)
Li 2016	Over-expression of cd200 predicts poor prognosis in cutaneous squamous cell carcinoma	Tumor grade, tumor stage, CD200 expression, gender, tumor size, age	Tumor grade, stage, CD200 expression	--	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
Manyam 2017	A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck	--	--	Immunosuppression	Immunosuppression
McDowell 2016a	Outcomes of cutaneous squamous cell carcinoma of the head and neck with parotid metastases	Age, immunosuppression, large node size	Age and immunosuppression	Immunosuppression and size of largest node	Immunosuppression

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
McDowell 2016b	P16-positive lymph node metastases from cutaneous head and neck squamous cell carcinoma: No association with high-risk human papillomavirus or prognosis and implications for the workup of the unknown primary	P16-positive lymph node metastases	--	P16-positive lymph node metastases	--
McLean 2013	Concurrent primary and metastatic cutaneous head and neck squamous cell carcinoma: Analysis of prognostic factors	Extracapsular spread and immunosuppression	Extracapsular spread and immunosuppression	--	--
Mizrachi 2013	Prognostic significance of nodal ratio in cutaneous squamous cell carcinoma of the head and neck	Nodal ratio and age	Nodal ratio and age	--	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
Oddone 2009	Metastatic cutaneous squamous cell carcinoma of the head and neck: The immunosuppression, treatment, extranodal spread, and margin status (item) prognostic score to predict outcome and the need to improve survival	Immunosuppression, location of nodes (parotid vs other), lymph node size, number of lymph nodes, P stage, N stage, extracapsular spread	Immunosuppression, extracapsular spread	--	--
Schmults 2013	Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: A 10-year, single-institution cohort study	Age, gender, tumor diameter <2, tumor grade, tumor depth, perineural invasion, lymphovascular invasion, tumor location (head and neck, ear, …)	Tumor depth and tumor grade	--	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
Shao 2014	Parotid metastatic disease from cutaneous squamous cell carcinoma: Prognostic role of facial nerve sacrifice, lateral temporal bone resection, immune status and p-stage	Immune status, extent of surgery, VII nerve involvement, and N-stage (neck)	Immune status	--	--
Sweeny 2014	Head and neck cutaneous squamous cell carcinoma requiring parotidectomy: Prognostic indicators and treatment selection	Parotid involvement, node involvement and perineural invasion	Node involvement	--	--
Tseros 2016	Prognostic significance of lymph node ratio in metastatic cutaneous squamous cell carcinoma of the head and neck	Lymph node ratio	Lymph node ratio	Lymph node ratio (for time to progression)	Lymph node ratio (for time to progression)

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	**Significant factors**	**Investigated factors**	**Significant factors**
Vasan 2018	Lymph node ratio as a prognostic factor in metastatic cutaneous head and neck squamous cell carcinoma	Lymph node ratio	Lymph node ratio	Lymph node ratio (for disease free survival)	Lymph node ratio (for disease free survival)

Abbreviations: mCSCC, metastatic cutaneous squamous cell carcinoma; OS, overall survival; TNM, tumor/node/metastasis staging system.

A16. CS Tables 10, 27, 28, 30, 31: Please clarify how the "balance" parameter is defined. Is this the standardised difference between intervention and comparator?

Sanofi response:

The balance parameter concerns an overall measure of balance across the considered covariates (i.e., ECOG, disease severity, age, gender, differentiation, tumor location and T stage in the ATT analysis; balance for prior systemic treatment was only considered in the ATC analysis): the difference of the absolute standardized difference for each of these covariates before and after applying weights were summed. Balance is a measure of how similar the covariate distributions of the two treatment groups are and is thus used as an indicator for the reduction in bias when estimating treatment effects resulting from the propensity score weighting.[5]

A17. Please describe the analysis software and provide the statistical code and any input data that are available for the propensity score based IPW indirect treatment comparison analyses.

Sanofi response:

The statistical code is provided as a supplementary material to this response. Please see document: ID3883 NICE CDF exit Clarification Question A17.

A18. CS section A.15.9 briefly summarises the STC and MAIC methodology. Please provide information on the statistical fit of the regression models to the data for each method.

Sanofi response:

The methodology for both the simulated treatment comparison (STC) and matching adjusted indirect comparison (MAIC) is the same as the original company submission for TA592 (as described in Section A.15.9 of the company submission).

[6]The model fits for both the core and extended STC regression models compared to both Jarkowski et al. 2016 and Sun et al. 2019 are provided in Table 5 to Table 7.As there is no statistic similar to the AIC which could be used to compare the fit of different

MAIC models, the model selection (i.e. core or extended) was based solely on the STC.

Table 5: Outcomes regression parameters from comparison of overall survival for cemiplimab (pooled EMPOWER-CSCC 1/Study 1423) versus chemotherapy with platinum using Jarkowski et al. 2016

Covariate	Core model		Extended model	
	HR (95% CI)	Beta (SE)	HR (95% CI)	Beta (SE)
Stage (locally advanced vs metastatic)	[redacted]	[redacted]	[redacted]	[redacted]
Location (head and neck vs other)	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male vs female)	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapy (yes vs no)	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]		[redacted]	

Note: Best fitting model with lower AIC indicated in green. **Abbreviations:** AIC, Akaike information criterion; CI, confidence interval; HR, hazard ratio; SE, standard error.

Table 6: Outcomes regression parameters from comparison of progression-free survival for cemiplimab (pooled EMPOWER-CSCC 1/Study 1423) versus chemotherapy with platinum using Jarkowski et al. 2016

Covariate	Core model		Extended model	
	HR (95% CI)	Beta (SE)	HR (95% CI)	Beta (SE)
Stage (locally advanced vs metastatic)	[redacted]	[redacted]	[redacted]	[redacted]
Location (head and neck vs other)	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male vs female)	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic therapy (yes vs no)	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]		[redacted]	

Note: Best fitting model with lower AIC indicated in green. **Abbreviations:** AIC, Akaike information criterion; CI, confidence interval; HR, hazard ratio; SE, standard error.

Table 7: Outcomes regression parameters from comparison of overall survival for cemiplimab (pooled EMPOWER-CSCC 1/Study 1423) versus best supportive care using Sun et al. 2019

Covariate	Core model		Extended model	
	HR (95% CI)	Beta (SE)	HR (95% CI)	Beta (SE)
Age (≤73 vs >73)	[redacted]	[redacted]	[redacted]	[redacted]
Stage (locally advanced vs metastatic)	[redacted]	[redacted]	[redacted]	[redacted]
Location (head and neck vs other)	[redacted]	[redacted]	[redacted]	[redacted]
Tumor stage (T stage 3 or 4 vs T stage <3)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance score (0 vs ≥1)	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male vs female)	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiation therapy (yes vs no)	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]		[redacted]	

Note: Best fitting model with lower AIC indicated in green. **Abbreviations:** AIC, Akaike information criterion; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; SE, standard error.

A19. PRIORITY QUESTION. Please confirm whether the statistical methods applied for the STC and MAIC analyses were identical to those used in the original company submission for TA592. If not, please explain what the differences were and provide a rationale for these.

Sanofi response:

The statistical methods applied for the STC and MAIC were identical to those described in the Company submission for TA592, document B, Section B.2.9.

A20. Please provide the statistical code for the STC and MAIC analyses, if different to that provided in clarification response A16 for the original appraisal TA592.

Sanofi response:

The statistical code for the STC and MAIC analyses are the same as those presented in Clarification response A16 for the Company submission of TA592.

A21. CS section A.7.2 (page 51) states "the results of the MAIC should be interpreted with caution as weights are not always well distributed for this analysis". Were the patient weights the same as reported in clarification response A12 of the original appraisal TA592? If not, please provide the updated weights.

Sanofi response:

Weights for the updated MAIC compared to both Jarkowski et al. 2016 and Sun et al 2019 are provided in Figure 5 to Figure 7 below. For Jarkowski et al. 2016, the core model adjusting for disease stage and location was used for both PFS and OS resulting in an effective sample size for the analysis of [redacted]. For Sun et al 2019 the extended model adjusted for age, disease stage, location, tumor stage, ECOG performance score, gender and prior RT, and resulted in a substantially reduced ESS of [redacted].

Figure 5: Weights used in matching-adjusted indirect comparison of overall survival for cemiplimab (pooled EMPOWER-CSCC 1/Study 1423) versus chemotherapy with platinum using Jarkowski et al. 2016 by time to event (effective sample size [redacted])

Figure 6 Weights used in matching-adjusted indirect comparison of progression-free survival for cemiplimab (pooled EMPOWER-CSCC 1/Study 1423) versus chemotherapy with platinum using Jarkowski et al. 2016 by time to event (effective sample size [redacted]

Figure 7: Weights used in matching-adjusted indirect comparison of overall survival for cemiplimab (pooled EMPOWER-CSCC 1/Study 1423) versus best supportive care using Sun et al. 2019 by time to event (effective sample size [redacted])

Proportional hazards assumption

A22. PRIORITY QUESTION. Please explain your interpretation of the Schoenfeld residuals plots and the log-log plots reported in Appendix E of the UK chart review report (reference 12). Please comment on those comparisons where the Schoenfeld residuals plots appear to show nonlinearity with time and the log-log plots appear to show crossing curves.

Sanofi response:

The Schoenfeld residuals and log-log plots show a trend for the proportional hazards assumption (PHA) being violated; according to the corresponding p-values this violation was not “statistically significant” (i.e., there is too much uncertainty to confirm that the PHA is violated). This uncertainty relates to the low sample size available from the chart review ([redacted]) as well as the low number of patients at risk after 12 months ([redacted] in the unweighted analyses). The KM curve also shows that, initially, the platinum-based chemotherapy (PBC) (Standard of care [SOC]) curve is above the cemiplimab curve, but after 7-8 months cemiplimab treated patients have better

outcomes and the curves diverge more constantly. Fewer deaths in the chart review cohort in the short run may be explained by selection bias within the chart review (i.e., inclusion of patients with a reasonable life expectancy). The chart review collected data from hospitals; however, feedback from a UK clinical advisory board conducted by Sanofi suggested that advanced CSCC patients may not initiate treatment in an hospital setting if their immediate life expectancy is poor, i.e. patients would be discharged for management of palliative care by their primary care physician. Thus, data for these patients would not have been collected within the chart review. Also, the mechanism of action of cemiplimab could result in delayed but more pronounced treatment benefit.

Further, visually, the log-log plots and KM curves appear to indicate a violation of the PHA. It should be noted that this is partly caused by 1 patient that received a high weight and died at log(time)=2 (approximately month 7 in the KM curve). Additionally, this visual test is also affected by the selection bias identified above. The few early events result in large steps in the log-log plot, which overemphasize the difference between the curves.

A potential solution is estimating time varying hazard ratios. This approach was not implemented because of the following:

1) low number of patients at risk, especially after 12 months in the chart review;

2) the non-proportionality of the hazards may be explained by a few patients with extreme weights as well as the above-mentioned selection bias.

3) The study focused on adjusting for all confounding variables, and this adjustment was incomplete in the analysis (i.e., insufficient data on prior radiotherapy). Therefore, more complicated approaches were not implemented, and the KM curves were considered as the main result.

A23. PRIORITY QUESTION. Please explain which statistical test was used to generate the p-values for assessing proportionality of hazards and how the p-values should be interpreted.

Sanofi response:

The Log-rank test was used to generate the p-values, please see Fleming et al. 2011 for interpretation of the p-value.[7]

A24. PRIORITY QUESTION. Given that proportionality of hazards is a key assumption for the analyses conducted, why was validity of the proportional hazards assumption not considered as a criterion for model selection?

Sanofi response:

For the ITC, KM curves were provided as a main result of the analyses which do not assume proportional hazards. However, KM curves are difficult to compare across multiple models and the hazard ratios comparing cemiplimab to SOC were provided as a summary measure to provide an overview of the relative treatment effects across models. Due to uncertainty with the PHA for the reasons highlighted in response to Clarification question A22, HRs were not incorporated in the CE model and a flexible modelling approach was used where each intervention was modelled independently for both PFS and OS.

A25. PRIORITY QUESTION. For those analyses where the proportional hazards assumption is not supported, please explain the implications for interpretation of the results.

Sanofi response:

The implication is that the HR is not a valid measure of the ITC results and that the KM curve should be used as primary result of the ITC. This approach is consistent with the CE model where each intervention was modelled independently for both PFS and OS (i.e., HRs were not used within the CE model).

HRQoL

A26. CS section A.15.10 provides a summary of HRQoL but no sample sizes are presented for the HRQoL outcomes. Please clarify how many patients provided the HRQoL data. If there were any missing HRQoL data please clarify whether these were accounted for and, if so, how.

Sanofi response:

As noted in CS section A.15.10, HRQoL data were collected through the October 2020 DCO. EORTC QLQ-C30 data collected from EMPOWER-CSCC 1 was mapped to the preference-based Euroqol-5 dimension 3-level (EQ-5D-3L) instrument to derive a utility for the pre- and post-progression health states by applying an established regression algorithm to the IPD from EMPOWER-CSCC 1. The same approach for the resubmission was adopted as for the initial submission, whereby base case utilities were estimated using the Longworth 2014 algorithm.

At the time of analysis, 193 patients had been enrolled in the study, of which [redacted] patients had completed the EORTC QLQ-30 at baseline, and had completed at least one complete questionnaire at any follow-up visit and were therefore included in the analysis dataset. Table 8 shows the number of questionnaires that had sufficient data at each follow-up time and for each scale at those time points. In many cases the questionnaires had missing values on at least one scale, and consequently, these could not be used in the mapping exercise.

Table 8: Number of observations available at each time point, October 2020 DCO

Timepoint	Number of questionnaires with sufficient data for the Longworth et al. (2014) and McKenzie and van de Pol (2009) algorithms
Baseline	[redacted]
Cycle 2, day 1	[redacted]
Cycle 3, day 1	[redacted]
Cycle 4, day 1	[redacted]
Cycle 5, day 1	[redacted]
Cycle 6, day 1	[redacted]
Cycle 7, day 1	[redacted]

Timepoint	Number of questionnaires with sufficient data for the Longworth et al. (2014) and McKenzie and van de Pol (2009) algorithms
Cycle 8, day 1	[redacted]
Cycle 9, day 1	[redacted]
Cycle 10, day 1	[redacted]
Cycle 11, day 1	[redacted]
Cycle 12, day 1	[redacted]
End of treatment	[redacted]

Safety

A27. Were there any differences in adverse events between the weight-based dose and fixed-dose groups within EMPOWER-CSCC 1 at the July 2021 data cut? If so, please describe these.

Sanofi response:

Formal analyses of these subgroups for the July 2021 DCO are not currently available, the analyses have been requested and will be shared with NICE/ERG upon receipt.

Safety is similar for CSCC patients treated with cemiplimab at 3 mg/kg and 350 mg Q3W IV. The safety profile of cemiplimab in study 1540 Groups 1,2,3 (Study 1540 Interim CSR, with a data cut-off date of 11 Oct 2020) [redacted]) I is similar to the established safety profile of cemiplimab in CSCC. [redacted] In the recent Development Safety Update Report (DSUR) with a data cut-off of 27 September 2021, no new safety signals were identified for cemiplimab in any study and for any posology. The sponsor monitors safety data continuously, including monthly study level reviews. No new safety signals in Groups 1, 2, or 3 have been observed to date.

A28. CS section A.15.11 provides a summary of selected adverse events. Please provide a full overview of the EMPOWER-CSCC 1 trial safety data for the July 2021 data cut, consistent with the level of detail provided in the original TA592 submission for Grade 3 and Grade 4 events.

Sanofi response:

Formal statistical analysis of safety data has not been performed for the July 2021 data cut. To supplement the safety analysis, results from a previous data cut (October 2020) have been provided below. Table 9 shows the TRTEAE's by system organ class and preferred term occurring in ≥ 2% of patients in any grade and all Grade 3/4/5 events (note, TA592 presented in Table 20 of Appendix F a summary of common TEAEs (≥5% of any grade or ≥1 grade 3/4/5 in any group). Please find

additional information related to Study 1540 in response to Clarification question A27.

Table 9: R281-ONC-1540: Summary of Treatment-Related Treatment-Emergent Adverse Events (TRTEAE) (≥ 2% in Any Grade and All in Grade 3/4/5) by System Organ Class and Preferred Term (Safety Analysis Set) - OCTOBER 2020 DCO

System Organ Class, n (%) Preferred Term, n (%)	Group 1 mCSCC LIBTAYO® 3 mg/kg Q2W (N = 59)		Group 2 laCSCC LIBTAYO® 3 mg/kg Q2W (N = 78)		Group 3 mCSCC LIBTAYO® 350 mg Q3W (N = 56)		Total (N = 193)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of TRTEAEs	[redacted]							
Number of patients with any TRTEAE ,- n (%)	[redacted]							
Skin and subcutaneous tissue disorders	[redacted]							
Pruritus	[redacted]							
Rash	[redacted]							
Rash maculo-papular	[redacted]							
Dry skin	[redacted]							
Psoriasis	[redacted]							
Autoimmune dermatitis	[redacted]							
Gastrointestinal disorders	[redacted]							
Diarrhoea	[redacted]							
Nausea	[redacted]							
Dry mouth	[redacted]							
Abdominal pain	[redacted]							
Colitis	[redacted]							

System Organ Class, n (%) Preferred Term, n (%)	Group 1 mCSCC LIBTAYO® 3 mg/kg Q2W (N = 59)		Group 2 laCSCC LIBTAYO® 3 mg/kg Q2W (N = 78)		Group 3 mCSCC LIBTAYO® 350 mg Q3W (N = 56)		Total (N = 193)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duodenal ulcer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oesophagitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proctitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Small intestinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antinuclear antibody increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

System Organ Class, n (%) Preferred Term, n (%)	Group 1 mCSCC LIBTAYO® 3 mg/kg Q2W (N = 59)		Group 2 laCSCC LIBTAYO® 3 mg/kg Q2W (N = 78)		Group 3 mCSCC LIBTAYO® 350 mg Q3W (N = 56)		Total (N = 193)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Polyarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

System Organ Class, n (%) Preferred Term, n (%)	Group 1 mCSCC LIBTAYO® 3 mg/kg Q2W (N = 59)		Group 2 laCSCC LIBTAYO® 3 mg/kg Q2W (N = 78)		Group 3 mCSCC LIBTAYO® 350 mg Q3W (N = 56)		Total (N = 193)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Respiratory,- thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury,- poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; PT = preferred term; Q2W = every 2 weeks; Q3W = every 3 weeks; SOC = system organ class; TRTEAE = treatment-related treatment-emergent adverse event.

Note: Data cut-off date: 11 October 2020.

All adverse events were coded using MedDRA Version 20.0.

A patient is counted only once for multiple occurrences within a system organ class/preferred term.

For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.

A29. Were any data available on adverse events for the UK chart review and SACT database cohorts? If so, please provide these for Grade 3 and Grade 4 events.

Sanofi response:

Adverse event data were not available from either the chart review or the SACT database cohort.

Section B: Clarification on cost-effectiveness data

Replication of model results

B1. PRIORITY QUESTION. The model submitted for the CDF review (with ICERs of £45,199 versus chemotherapy and £52,539 versus BSC) does not appear to be consistent with the revised company base case ICERs after technical engagement that were presented at the committee meeting and are cited in the NICE Terms of Engagement for the CDF review (ICERs of £45,693 versus chemotherapy and £47,463 versus BSC).

(a) Please explain the discrepancy in the version of the model used as the basis for the CDF review. Please re-run the analyses with the correct starting version of the model base case.

(b) Please revise the functionality within the sheet "Model Parameters" to revert the updated CDF model to the correct starting ICERs (that is, '[ID1367 ERG analysis CAA price post FAC v0.1 28.01.19 (ACIC)]' that incorporates the revised model assumptions following technical engagement), for model validation.

Sanofi response:

a) The model submitted for the CDF review aligns with the model ('[ID1367 ERG analysis CAA price post FAC v0.1 28.01.19 (ACIC)] provided alongside the terms of engagement for this appraisal. However, for decision making purposes the model ID1367_Cemiplimab CEM__updated_12.03.2019 was used. As discussed in the Clarification question meeting an updated analysis will be provided to NICE/ERG when it becomes available

b) An updated version of the economic model (ID1367_Cemiplimab CEM__updated_12.03.2019) was submitted in response to technical engagement for the original appraisal. The ICERs presented at the committee meeting reflected this model rather than the model provided to us alongside the terms of engagement.

Sanofi will provide an updated model so that these ICERs can be replicated by the ERG the week commencing February 6th, 2022.

B2. PRIORITY QUESTION. Section A.9: CS Table 15 states the company model uses a second-order fractional polynomial (p0 p-1) to extrapolate the overall survival for chemotherapy. This is inconsistent with the Excel model that uses a log-logistic curve to extrapolate OS for chemotherapy in the base case. Please explain this inconsistency.

Table 15 contains a reporting error, the correct extrapolation for OS for chemotherapy is the log-logistic, as outlined in Section A8.3.2 of the Company submission. Text in Section A.8.3.2 has also been updated to reflect the correct extrapolation.

B3. PRIORITY QUESTION. The ERG are unable to replicate the company's reported cost effectiveness results for the company base case and scenario analyses. Please explain the discrepancies, as reported in the tables below:

(a) CS section A10. Base case ICERs

ICERs for the base case	Results reported by the company	Results obtained by the ERG
cemiplimab vs chemo. (PAS price)	£36,163	£36,814
cemipimab vs BSC (PAS price)	£29,438	£28,859
cemiplimab vs chemo. (list price)	[redacted]	[redacted]
cemipimab vs BSC (list price)	[redacted]	[redacted]

(b) Results reported in CS Table 16: ICER vs chemotherapy (PAS price)

Analysis	Results reported by the company	Results obtained by the ERG
1 a. cemiplimab: log-normal for OS extrapolation, Weibull for PFS extrapolation, October 2017 EMPOWER-CSCC 1 data, 22-month stopping rule, 36-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016	£40,233	£38,085
1 b. cemiplimab: log-normal for OS extrapolation, Weibull for PFS extrapolation, October 2017 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 36-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016	£39,536	£39,506

Analysis	Results reported by the company	Results obtained by the ERG
6. cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 60-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016	£39,093	£35,093
7. cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 60-month hazard switching assumption; chemotherapy: log-logistic for OS extrapolation, chart review	£36,163	£36,814

(c) Results reported in CS Table 17: ICER vs BSC (PAS price)

Analysis	Results reported by the company	Results obtained by the ERG
1 a. cemiplimab: log-normal for OS extrapolation, Weibull for PFS extrapolation, October 2017 EMPOWER-CSCC 1 data, 22-month stopping rule, 36-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016	£43,590	£41,436
1 b. cemiplimab: log-normal for OS extrapolation, Weibull for PFS extrapolation, October 2017 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 36-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016	£42,891	£42,861
3. cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 60-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016	£38,007	£48,217
4. cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 60-month hazard switching assumption; chemotherapy: log-logistic for OS extrapolation, chart review	£29,438	£28,859

(d) Results reported in CS section A.12 (CS Table 20)

Analysis	vs Chemotherapy		vs BSC	
	Company	ERG	Company	ERG
Base case	£36,163	£36,814	£29,438	£28,859
Survival comparator with Jarkowski et al.	£37,491	£35,093	£39,340	£38,006

SACT baseline characteristics	£37,775	£38,376	£30,953	£30,332
No treatment waning	£26,263	£26,244	£24,663	£24,115
Treatment waning between 60 and 96 months	£32,466	£32,745	£26,002	£25,343

Sanofi response:

The Excel workbook “ID3883 NICE CDF exit ERG Clarification Questions - Section B” details the model settings for each scenario are provided as supplementary material alongside the clarification response.

Note. On review of the results included in the Company submission an error was identified for Scenario analysis 1: Survival for comparator arms informed by Jarkowski et al. 2016, as presented in Table 20. Revised ICERs will be provided along with the updated model the week commencing February 6th, 2022.

Below, in response to B3 b, c and d, please find below Table 16, 17 and 20 from the dossier relating to the excel workbook. These include the correction to Scenario analysis 1 as noted above.

Table 16: Cost-effectiveness results for cemiplimab versus chemotherapy (deterministic, PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (cemiplimab: log-normal for OS extrapolation, log-normal for PFS extrapolation, October 2017 EMPOWER-CSCC 1 data, *24-month stopping rule, ERG resource use costs, CDF entry MAA*, 36-month hazard switching assumption; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,693	£45,693
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence (*cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data,* 24-month stopping rule, ERG resource use costs, *CDF exit MAA, 60-month hazard switching assumption*; chemotherapy: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,093	£35,093
Cost-effectiveness analysis 3: New company base case (cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, ERG resource use costs, 60-month hazard switching assumption; chemotherapy: *log-logistic for OS extrapolation, chart review*)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
Platinum-based Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,163	£36,163
Key: CSCC, cutaneous squamous cell carcinoma; ERG, Evidence Review Group; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.								

Table 17: Cost-effectiveness results for cemiplimab versus BSC (deterministic, PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (cemiplimab: log-normal for OS extrapolation, October 2017 EMPOWER-CSCC 1 data, 24-month stopping rule, 36-month hazard switching assumption; BSC: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,463	£47,463
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence (*cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data,* 24-month stopping rule*, 60-month hazard switching assumption*; BSC: Gompertz for OS extrapolation, Jarkowski 2016)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,007	£38,007
Cost-effectiveness analysis 3: New company base case (cemiplimab: log-normal for OS extrapolation, FP (p0, p-1) for PFS extrapolation, July 2021 EMPOWER-CSCC 1 data, 24-month stopping rule, 60-month hazard switching assumption; BSC *log-logistic for OS extrapolation, Sun 2019*)								
Cemiplimab	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,438	£29,438
Key: CSCC, cutaneous squamous cell carcinoma; ERG, Evidence Review Group; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.								

Table 20: Key scenario analyses (PAS price) – B.3.8.3 (Table 49, page 166)

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base case ICER vs.	
			Platinum-based chemotherapy	BSC
Base case			£36,163	£29,438
Survival for comparator arms informed by Jarkowski et al. 2016 *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with Jarkowski comparator data, OS Gompertz, PFS Weibull.*	Jarkowski survival data used for comparator OS	Alternative data source for comparator estimates	£36,446	£39,340
Use of ATC propensity score model 1 *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with ATC (cemiplimab), model 1 data, OS log-normal, PFS FP (p0, p-1).*	Analysis matching trial data to integrated chart review data	As trial data had more variability in ECOG and prior systemic therapy and a higher sample size, this model allows for inclusion of these prognostic factors. The ATC model 1 was used to match the best fitting ATT analysis used in the base case	£39,346	NA
Full ATT propensity score model *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with ATT (chart review), full model data, OS log-normal, PFS FP (p0, p-1).*	Propensity score model including ECOG status and Tumour location as prognostic factors	Insufficient overlap of variables, specifically, ECOG status, excluded these from the base case analyses. Full model explores impact of inclusion	£36,621	NA
SACT baseline characteristics *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with SACT baseline characteristics.*	SACT population age and gender data	Exploratory scenario to estimate cost-effectiveness results based on limited real-world data from NHS England clinical practice	£37,775	£30,953

No waning of treatment benefit (continuation of hazard trend) *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with continuation of hazard trend for cemiplimab.*	No loss of treatment effect	Exploratory scenario investigating no loss of treatment effect	£26,263	£24,663
Treatment waning applied between 60 and 96 months *Cost-effectiveness analysis 3 presented in Table 16 and Table 17 with gradual treatment waning between 60 and 96 months for cemiplimab.*	Gradual loss of treatment effect between 60 and 96 months	Exploratory scenario investigating a gradual loss of treatment effect	£32,466	£26,002

Section C: Textual clarification and additional points

C1. CS Table 24 says "pooled EMPOWER-CSCC 1/Study 1623". Is this a typographic error (we assume 1623 should read 1423)? If not please explain what study 1623 is.

Sanofi response:

This is a typographical error. The text should read EMPOWER CSCC-1/ Study 1423and should read 1423.

C2. Please provide footnotes a and b for CS Table 26.

Sanofi response:

Footnotes and key from Table 26 were missing erroneously, please see below.

Characteristic		Chart review, integrated UK cohort	Chart review, audit UK cohort
N		[redacted]	[redacted]
Disease severity, n (%)	laCSCC, n (%)	[redacted]	[redacted]
	mCSCC	[redacted]	[redacted]
Age, median (range)		[redacted]	[redacted]
Gender, n (%)	Male	[redacted]	[redacted]
Differentiation, n (%)	Well	[redacted]	[redacted]
	Moderate/Poor/ Undifferentiated	[redacted]	[redacted]
	Undetermined	[redacted]	[redacted]
Tumor location, n (%)	Head and Neck	[redacted]	[redacted]
	Trunk	[redacted]	[redacted]
	Extremities	[redacted]	[redacted]
T stage, n (%)	T0	[redacted]	[redacted]
	Tis	[redacted]	[redacted]
	Tx	[redacted]	[redacted]
	T1	[redacted]	[redacted]
	T2	[redacted]	[redacted]
	T3	[redacted]	[redacted]
	T4	[redacted]	[redacted]
ECOG performance status, n (%)	0[a]	[redacted]	[redacted]
	1[a]	[redacted]	[redacted]
Prior systemic therapy, n (%)		[redacted]	[redacted]

Characteristic	Chart review, integrated UK cohort	Chart review, audit UK cohort
Prior radiation, n (%)	[redacted]	[redacted]

Note: a) measured from start of first line of therapy; b) prior radiation includes only those patients who have a confirmed date of administration – those patients in the chart review who were indicated to have received palliative radiation but with no date of administration defined have not been included in the count. Integrated audit population is the original chart review data combined with the audit.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; UK, United Kingdom.

C3. 1. The heading of CS Table 17 states that the comparator is BSC, but scenarios 1a, 1b, 2 and 3 in the table refer to OS settings for chemotherapy. Please explain this inconsistency.

Sanofi response:

A typographical error, this should read**: BSC: Gompertz for OS extrapolation**.

Questions raised during the Clarification meeting (20220131)

1. OBC abbreviation in Table 5 of ITC report

This is a typo and should read PBC.

2. Data cut for study 1423

The 2019 data cut from Study 1423 was used for the analysis

3. Price of PFS in the model (£687.42) and report (£1,241.65)

Table 42 of the Company submission contains a typo, the PFS the pre-progression costs should read £687.42. The difference lies in the setting applied in cell C75 of the "Model Parameters" tab. If assuming the Company resource use from the Company submission for TA592, the cost is £1,241.65. However, when applying the ERG scenario assuming reduced resource use, the cost is £687.42.

4. Rationale for not using the MVR results in the CEM

The multivariable regression models (MVR) were used as a means to assess the validity of the propensity score methods. Large discrepancies between the approaches would imply that one or both of them were not able to estimate accurate treatment effects, while broad similarities lend weight to the conclusion that the models are valid. With the MVR approach, regression models were fitted on each dataset independently. The individual differences in the predictions for the two potential outcomes were then averaged across all individuals to obtain an estimate of the treatment effect[8,9]; this estimate is a conditional effect (i.e. one based on specific values of the covariates). This differs from the marginal (i.e. population level) estimate obtained from the propensity score models. The marginal estimate and standard errors of the treatment effect in the MVR were derived using bootstrapping; however, in many of the bootstrap samples the procedure produced singular matrices i.e. samples that contained only a single level of a categorical variable within a dataset (e.g., ECOG, or prior systemic treatment), which precluded the fitting of a model on these variables (see Table 10 below). This was expected because the sample size of patients with an ECOG PS of 0 and/or prior treatment low in the chart review data. Consequently, there was uncertainty whether the treatment effect estimate was truly marginal, especially

for the full model for which most bootstrap samples had singular matrices. This issue was less of a limitation for the best fitting MVR, which included only “disease severity (laCSCC, mCSCC)”, tumor location and ECOG (457 of the 10,000 bootstrap samples could not be fitted using the best fitting model). However, variable selection may be inaccurate in small datasets. Further, these “singular matrices” likely concern more extreme bootstrap samples, so excluding them from the marginal estimate likely resulted in an underestimate of the 95% CIs of the relative treatment effects. As a consequence of this, the results from the MVR were not considered sufficiently robust for inclusion in the cost-effectiveness model.

Table 10: Results of the multivariable regression analyses

	Full model	Full model, excluding prior systemic, ECOG	Backward selection
HR (95% CI) (cemiplimab vs PBC SoC) – conditional model	[redacted]	[redacted]	[redacted]
HR (95% CI) (cemiplimab vs OBC SoC) - marginal	[redacted]	[redacted]	[redacted]
Failed models: bootstrap samples with singular matrix[a]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]
Characteristic			
Disease severity (laCSCC, mCSCC)	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]
Differentiation	[redacted]	[redacted]	[redacted]
Tumor location (H&N, trunk, extremities)	[redacted]	[redacted]	[redacted]
T stage (TNM)	[redacted]	[redacted]	[redacted]
ECOG performance status	[redacted]	[redacted]	[redacted]
Prior systemic therapy	[redacted]	[redacted]	[redacted]
Prior radiation	[redacted]	[redacted]	[redacted]

Notes: a) 10,000 bootstrap samples were used to estimate the marginal effect. **Abbreviations:** AIC, Akaikes information criteria; CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; MVR, multivariable regression; N, No; NA, not applicable; T (TNM), T stage of the TNM Classification of Malignant Tumors; Soc, standard of care; Y, yes.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592) [ID3883]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Association of Dermatologists (BAD)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its Members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of	**No**

manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main indication for this treatment is for advanced cutaneous squamous cell carcinoma (cSCC) that have spread locally, regionally or distant and are no longer curable by surgery and/or radiotherapy (i.e. to stop/prevent progression)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Any tumour reduction that alleviates pain and patient distress is worthwhile. Prevention of tumour progression (i.e. stable disease) is also a worthwhile aim in this most distressing of diseases because patients get large fungating tumours that weep, bleed and smell and are often very painful.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, very much so. There is no effective treatment for advanced cSCC other than surgery/radiotherapy and once these have failed, this immunotherapy is the next best choice. As the previous NICE review stated, "Living with advanced unresectable cutaneous squamous cell carcinoma is physically and emotionally challenging, and there is a high unmet need for new treatments".
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	There is no good treatment other than cemiplimab once the cancer is beyond surgery and/or radiotherapy so this condition is currently treated by best supportive care where cemiplimab fails or is contraindicated. Currently, cemiplimab is available via the Cancer Drugs Fund. Early cSCC is treated by excision surgery. More advanced and metastatic cSCC may be treated with radiotherapy after surgery.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma 2020 • Australian clinical practice guidelines for keratinocyte cancer 2019 • American guidelines of care for the management of cutaneous squamous cell carcinoma 2018 • SIGN management of primary cutaneous squamous cell carcinoma 2014 **N.B.** Please note that the 2015 European guideline cited in the final scope has since been superseded by a newer iteration in 2020.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Within the UK, very few patients will be offered EGFR inhibitors or chemotherapy. Because of our good experience with immunotherapy for metastatic melanoma, most oncologists would consider cemiplimab as standard of care if surgery/radiotherapy has failed. We do not believe there would be much equipoise on this. The main discussion would be cemiplimab or best supportive care. This decision would often depend on how old and frail the patient is, and whether they have significant co-morbidities. For instance, solid organ transplantation (SOTR) would be a contraindication.
• What impact would the technology have on the current pathway of care?	It would provide an alternative to best supportive care and would give approximately 50% of patients with advanced cSCC the possibility of durable remission.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it is already used as current care in NHS clinical practice.
• How does healthcare resource use differ between the technology and current care?	Cemiplimab is expensive, but there is currently no alternative for these patients, and many will do well on this treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary	Secondary care, oncology specialists, under the auspices of SSMDTs.

care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It would be sensible to audit use and outcomes if formally introduced. All SSMDTs should already have oncologists with the knowledge to prescribe, monitor and manage cemiplimab and its side effects. Currently, it is available via the Cancer Drugs Fund.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, we would expect significant meaningful benefits from having this treatment available. It is already proving highly beneficial in more than 50% of patients.
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or	Cemiplimab is contraindicated for SOTR recipients because of risk of provoking allograft rejection. However, it is being used in SOTR (internationally) when there are no other options, and it can be possible to prevent the rejection episode so we think even this use may become widespread. Cemiplimab should

less effective (or appropriate) than the general population?	also be used with caution in those with autoimmune disease.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The same – already part of current care, and already using the same class of drug (anti-PD1 inhibitors) for melanoma and other cancers so healthcare professionals are very experienced with its use.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Similar to melanoma and Merkel cell carcinoma. Currently, 2 years' treatment for SCC with cemiplimab in CDF, which is reasonable. There is no time limit for avelumab in Merkel cell carcinoma and varying rules

Do these include any additional testing?	for melanoma.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, this is a very important point. Most patients with advanced cSCC die from horrendous loco-regional disease, not from distant metastases. Therefore, the most important (i.e. primary) outcomes to consider are progression-free survival (PFS) or stabilisation of loco-regional disease – not overall survival (which is important, but secondary to these). You will seriously underestimate the benefit by just looking at the QALY calculation.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, it is innovative in that no other treatments are available for advanced cSCC. However, it is not a new treatment as has been in use through the cancer drugs fund for the past 2 years.
• Is the technology a 'step-change' in the management of the	Yes, we believe so.

condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Yes – complete response or even just control of local progression is an extraordinary advance on any previous therapies. 1. Those who have failed chemotherapy. 2. Those who, due to their comorbidities or performance status, cannot have chemotherapy. 3. Those who for many reasons cannot attend radiotherapy. 4. Those who have been treated with radiotherapy before.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Overall, single-agent anti-PD1 are well tolerated. There are well-recognised, immune-related adverse events (IRAE) with cemiplimab as with all immune checkpoint inhibitors. Some of these are serious and may lead to a life-long need for replacement with, e.g. hormones. UK-based oncologists are very familiar with these IRAEs and usually they can be 'managed' adequately, although sometimes they will lead to withdrawal of the treatment. These immune checkpoint inhibitors are used very extensively for melanoma, so skin cancer oncologists are especially experts at using these treatments and at managing any adverse events.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK	Yes – if anything, real-world experience with cemiplimab shows improved outcomes compared with the clinical trials.

clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	See above.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcome is PFS as discussed above (see Q15). The emphasis on overall survival for most cancer trials is less appropriate for cSCC as explained in Q15. The definitive RCT did look at PFS as well as OS.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, PFS or stabilised loco-regional disease do predict long-term clinical outcome adequately. See response to Q15.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not really – the IRAEs have a large evidence-base related to use of pembrolizumab and nivolumab for melanoma. Real-world data with cemiplimab appears similar to AEs seen with these two commonly used anti-PD1 inhibitors.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Our comments in Q15 are very important and need to be taken on board when assessing benefit from use of this treatment. We do not feel that the QALY calculation is appropriate – the importance of loco-regional disease and loco-regional progression as the major cause of morbidity and mortality for this cancer may not be found by a systematic review of the trial evidence. It will depend what outcomes were reported.

20. How do data on real-world experience compare with the trial data?	The real-world data suggests benefit from cemiplimab is at least as good as that shown in the clinical trials. Experience shows it to be very well tolerated, safe in the predominantly elderly population, and effective.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No – the most important 'issue' is that many of these patients with cSCC are elderly and frail and therefore may not wish to have systemic treatment. Salvage surgery and radiotherapy is likely to be very debilitating and these elderly/frail patients may not be able to tolerate this standard of care. Whilst the potential IRAEs are a possible contraindication for elderly/frail patients, it may be shown in the future that they are more able to tolerate cemiplimab than to tolerate the prior surgery or radiotherapy.
21b. Consider whether these issues are different from issues with current care and why.	The IRAEs are very different from standard of care with surgery +/- radiotherapy. There are arguments that the elderly/frail may be less likely to respond to checkpoint inhibitors, but equally, they may get benefit with reduced IRAEs. The fitness, or not, of elderly/frail patients for these immunotherapies must be judged on an individual basis by the clinician with responsibility for the patient.
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Cemiplimab is a very beneficial treatment for advanced cSCC – outcomes are improved in at least 50% of treated patients, possibly more. Any benefit shown is often very durable as shown with checkpoint inhibitor immunotherapy in melanoma.
- There is no other treatment that shows durable benefit for patients with advanced cSCC once surgery/radiotherapy has failed. Any benefit from targeted therapies such as EGFR inhibitors are very short-lived and poorly tolerated. The only appropriate alternative is best supportive care.
- The use of overall survival as the health-related benefit in the QALY calculation is not appropriate for this disease. In these patients, the substantial morbidity (and mortality) is from progressive loco-regional disease. The appropriate outcome for cSCC is progression-free survival (or stabilisation of regional disease). This should be taken into account when making the QALY calculation.
- The immune-related adverse events seen with cemiplimab are also seen commonly with pembrolizumab and nivolumab. Skin cancer oncologists are already expert at using these immune checkpoint inhibitors for melanoma. Consequently, the use of cemiplimab for cSCC falls within their expertise and, indeed, cemiplimab is already in clinical use for advanced cSCC.
- Cemiplimab is not suitable for organ transplant recipients (OTR) as it can trigger rejection of the allograft. There is active research investigating other immunotherapies that might be suitable for OTR, but in the absence of these, anti-PD1 inhibitors are occasionally being used in OTR and clinicians are developing strategies to prevent rejection. Until these anti-rejection regimens are established, this treatment should usually be avoided in OTR subject to the comments in Q12.

Thank you for your time.

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NATIONAL DISEASE REGISTRATION SERVICE

NHS Digital

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma – data review

Commissioned by NHS England and NHS Improvement

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS Digital (NHSD). Its purpose is to collect and quality-assure high-quality, timely data on a wide range of diseases and provide robust surveillance to monitor and detect changes in health and disease in the population.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
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National Disease Registration Service
NHS Digital (NHSD)
The Leeds Government Hub
7&8 Wellington Place
Leeds
LS1 4AP

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1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma. The appraisal committee highlighted clinical uncertainty around baseline characteristics of patients and estimates of duration of treatment in the evidence submission. As a result, they recommended the commissioning of cemiplimab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned NHS Digital (NHSD) to evaluate the real-world treatment effectiveness of cemiplimab in the CDF population, during the managed access period. This report presents the results of the use of cemiplimab in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and NHSD partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99% of patients and 93% of patient outcomes reported in the SACT dataset. NHSD and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for cemiplimab for metastatic or locally advanced cutaneous squamous cell carcinoma in the CDF. Patient NHS numbers were used to link Blueteq applications to NHSD's routinely collected SACT data to provide SACT treatment history.

Between 2 July 2019 and 1 March 2021, 393 applications for cemiplimab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 352 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS).[1]

Results

352 (99%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 8 months [95% CI: 6.2, 9.3] (243 days). 57% of patients were still receiving treatment at 6 months [95% CI: 51%,62%], 39% of patients were still receiving treatment at 12 months [95% CI: 33%, 44%], 33% of patients were still receiving treatment at 18 months [95% CI: 26%, 39%].

At data cut off, 59% (N=207) of patients were identified as no longer being on treatment. Of these 207 patients, 24% (N=49) of patients stopped treatment due to progression, 9% (N=19) of patients stopped treatment due to acute toxicity, 4% (N=9) of patients chose to end their treatment, 16% (N=34) of patients died not on treatment, 9% (N=18) of patients died on treatment, 3% (N=6) of patients completed treatment as prescribed, 3% (N=7) of patients stopped treatment due to COVID, 10% (N=21) of patients were treated palliatively and did not benefit from the treatment they received, 17% (N=35) of patients were treated palliatively and did benefit from the treatment they received and 4% (N=9) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

The median overall survival (OS) was 21 months[a] (639 days). OS at 6 months was 75% [95% CI: 70%, 79%], 12 months OS was 63% [95% CI: 58%, 68%], OS at 18 months was 56% [95% CI: 49%, 61%] and OS at 24 months was 46% [95% CI: 37%, 54%].

A treatment duration sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients treated with cemiplimab for metastatic or locally advanced cutaneous squamous cell carcinoma in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with cemiplimab for this indication.

[a] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Introduction

Cutaneous squamous cell carcinoma (cSCC) (ICD-10: C44.9), a non-melanoma skin cancer, represents one of the most common cancers diagnosed, with an increasing incidence rate. In 2018, 83,850 patients were diagnosed with cSCC in England (males 45,820, females 38,030).[2]

1. Cemiplimab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic cutaneous squamous cell carcinoma in adults when curative surgery or curative radiotherapy is not appropriate. It is recommended only if the conditions in the managed access agreement are followed.[3]

2.Background to this report

The NHS Digital and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and NHS Digital's (NHSD's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the NHSD and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by NHSD. This includes NHS England and NHS Improvement commissioning NHSD to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England.[4] From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

NHSD analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Disease Registration Service (NDRS), which is part of NHSD.

NICE Appraisal Committee review of cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma [TA592].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of cemiplimab (Sanofi) in treating metastatic or locally advanced cutaneous squamous cell carcinoma [TA592] and published guidance for this indication in August 2019[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma through the CDF for a period of 24 months, from Jul 2019 to Jul 2021.

During the CDF funding period, results from an ongoing clinical trial (EMPOWER-CSCC 1)[7] evaluating cemiplimab in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the EMPOWER-CSCC 1 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for cemiplimab for metastatic or locally advanced cutaneous squamous cell carcinoma in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the EMPOWER-CSCC 1 clinical trial[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection:

- the baseline characteristics of patients
- treatment duration (from the start of a patient's first treatment with cemiplimab)
- generalisability to UK clinical practice

OS was not an area of clinical uncertainty but has been included in this report.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, NHSD and the company (Sanofi) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of cemiplimab. It also detailed the eligibility criteria for patient access to cemiplimab through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for cemiplimab, approved through Blueteq® and followed up in the SACT dataset collected by NHSD.

3. Methods

CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NHSD has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS Digital (NHSD), through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England and NHS Improvement.

NHSD collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Cemiplimab clinical treatment criteria

1. Cemiplimab as monotherapy is recommended for use in the Cancer Drugs Fund (CDF) for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. Cemiplimab will be stopped at 2 years of treatment, on disease progression or if there is unacceptable toxicity (whichever occurs first)

2. Patient has a histologically- or cytologically-confirmed diagnosis of cutaneous squamous cell carcinoma

3. Patient has either locally advanced disease or metastatic disease and is not a candidate for curative surgery or curative radiotherapy. Record whether the disease is locally advanced or metastatic and if metastatic, whether the disease is nodal only or includes distant spread:

- locally advanced disease which results in the patient not being a candidate for curative surgery or curative radiotherapy or,
- metastatic disease with spread which is nodal only or,
- metastatic disease with spread that includes distant metastasis (e.g. lung, liver, bone etc)

4. Patient does not have a contra-indication to being treated with cemiplimab
    - immunocompromised patients were not included in the main cemiplimab clinical study
    - cemiplimab should be used with caution in immunosuppressed patients and if cemiplimab is being administered to an immunocompromised patient, then a full evaluation and discussion with the patient of the benefits and the risks of treatment with cemiplimab (e.g. rejection of a solid organ transplant) must be undertaken

5. Cemiplimab is to be given solely as monotherapy

6. Treatment with cemiplimab will continue until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent or for a maximum treatment duration of 2 years (or 35 3-weekly cycles of cemiplimab), whichever occurs first
    - In those patients transferring from the Sanofi compassionate access scheme (see section 3.3), a maximum total treatment duration of 2 years of treatment applies

7. Patient is fit for treatment with cemiplimab and has an ECOG performance status score of 0 or 1

8. Patient has no symptomatically active brain metastases or leptomeningeal metastases

9. Patient has not received prior treatment with an anti-PD-1, anti-PD-L1,anti-PD-L2, anti CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless the patient has been entered into the Sanofi cemiplimab compassionate access scheme and all other treatment criteria are fulfilled (e.g. ECOG performance status)

10. A formal medical review as to whether treatment with cemiplimab should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment

11. Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow any immune toxicities to settle

12. Clinician is fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to anti-PD-1 treatments including pneumonitis, colitis, nephritis, endocrinopathies, hepatitis and cutaneous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

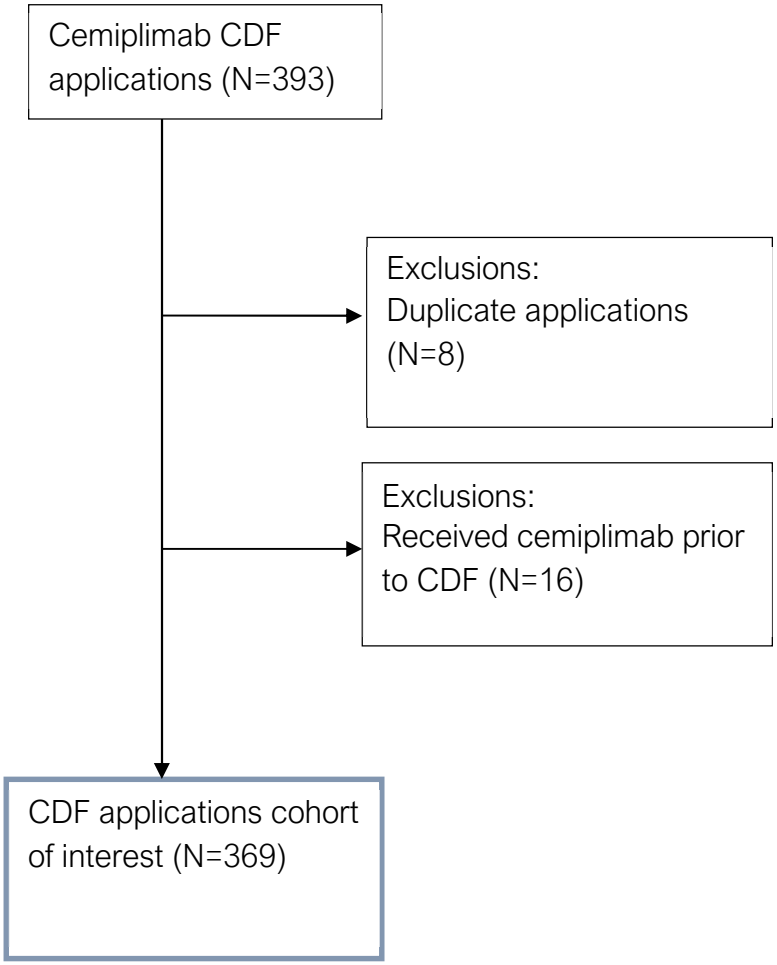
Initial CDF cohorts

The analysis cohort is limited to the date cemiplimab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 2 July 2019 to 1 March 2021. A snapshot of SACT data was taken on 7 August 2021 and made available for analysis on 13 August 2021 and includes SACT activity up to the 30 April 2021. Tracing the patients' vital status was carried out on 6 September 2021 using the Personal Demographics Service (PDS).[1]

There were 393 applications for CDF funding for cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma between 2 July 2019 and 1 March 2021 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 385 unique patients. Sixteen patients were excluded as they received cemiplimab prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma between 2 July 2019 and 1 March 2021



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for durvalumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example, a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Cemiplimab is administered intravenously. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that treatment administration has taken place on a specified date. A duration of 20-days has been added to the final treatment date for all patients, this represents the duration from a patient's last cycle to their next[9]. Cemiplimab is a 21-day cycle consisting of one administration.

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61
- there is no further SACT records for the patient following a three-month period

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

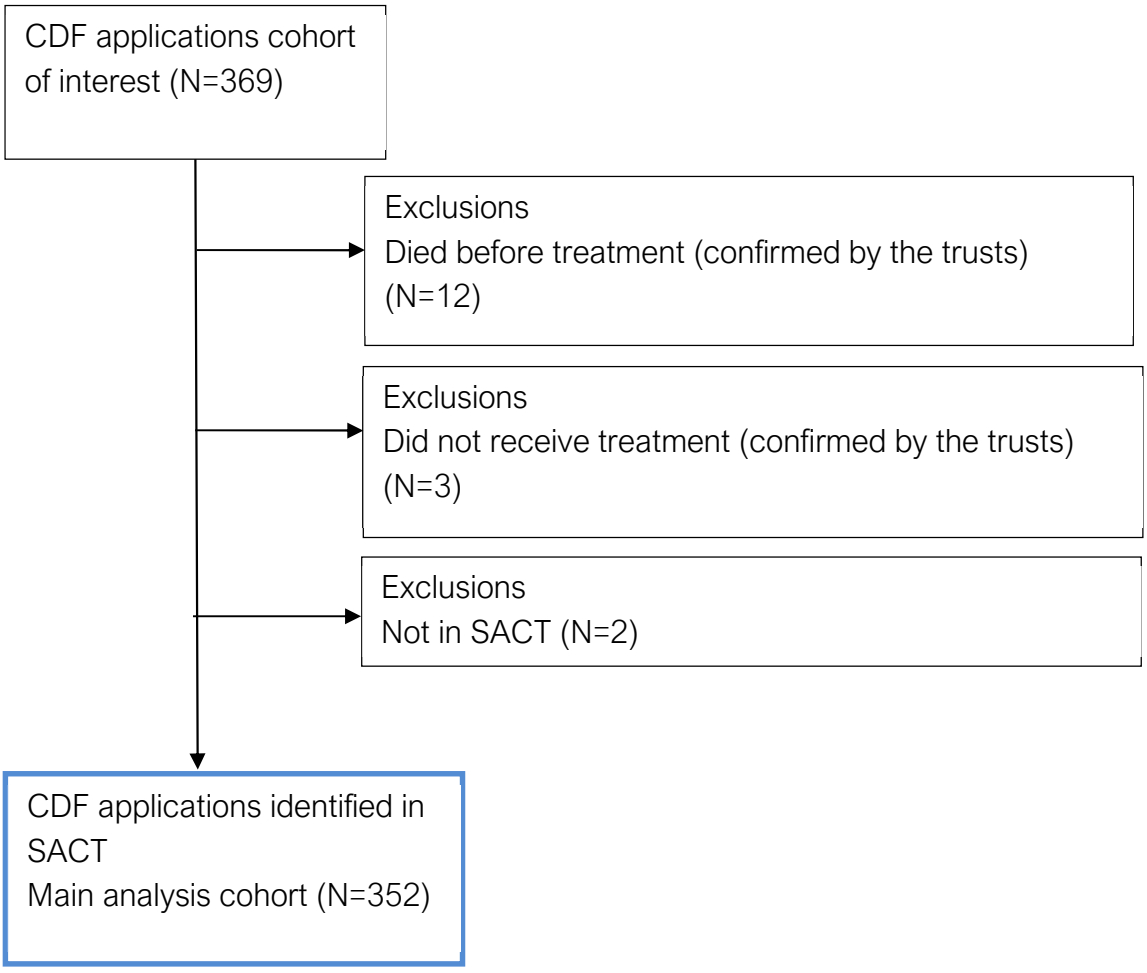
- dead (event):
    - at the date of death recorded on the PDS
- alive (censored):
    - at the date patients were traced for their vital status as patients are confirmed as alive on this date

4. Results

Cohort of interest

Of the 369 applications for CDF funding for cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma, three patients did not receive treatment, 12 patients died before treatment and two patients were missing from SACT[b] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma between 2 July 2019 and 1 March 2021



[b] Of the three patients that did not receive treatment and the 12 that died before treatment, all were confirmed by the relevant trust by the NHSD data liaison team.

A maximum of 354 cemiplimab records are expected in SACT for patients who were alive, eligible, and confirmed to have commenced treatment (Figure 2). 99% (352/354) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 86% complete.

Table 1: Completeness of key SACT data items for the cemiplimab cohort (N=352)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	86%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with cemiplimab in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 207 patients. Of these, 193 (93%) have an outcome summary recorded in the SACT dataset.

Table 2. Completeness of outcome summary for patients that have ended treatment (N=207)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	84%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Locally advanced or metastatic disease was 100% complete and immunocompromise was 93% complete.

Table 3: Completeness of key Blueteq data items for the cemiplimab cohort (N=352)

Variable	Completeness (%)
Locally advanced or metastatic disease	100%
Immunocompromise	93%

Patient characteristics

The median age of the 352 patients receiving cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma was 77 years. The median age in males and females was 77 and 76 years respectively.

Table 4. Patient characteristics (N=352)

Patient characteristics[c]			
		N	%
Sex	Male	262	74%
	Female	90	26%
Age	<40	3	1%
	40 to 49	9	3%
	50 to 59	26	7%
	60 to 69	52	15%
	70 to 79	137	39%
	80+	125	36%
Performance status	0	64	18%
	1	223	63%
	2	14	4%
	3	0	0%
	4	0	0%
	Missing	51	14%

[c] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows the distribution of Blueteq data items with 49% (N=172) of patients having locally advanced disease, 26% (N=92) of patients having metastatic disease with distant spread, 22% (N=77) of patients having metastatic disease with nodal spread and 3% (N=11) of patients having metastatic disease with spread that includes distant metastasis.

Majority of patients, 88% (N=311) were not immunocompromised, 4% (N=15) of patients previously received a solid organ transplant or have an autoimmune disease and 7% (N=26) of patients did not have a value captured in Blueteq.

Table 5: Distribution of key Blueteq data items (N=352)

Blueteq data itemsd		N	%
Locally advanced or metastatic disease	Locally advanced disease	172	49%
	Metastatic disease with distant spread	92	26%
	Metastatic disease with nodal spread	77	22%
Immunocompromise	Metastatic disease with spread that includes distant metastasis	11	3%
	No immunocompromise	311	88%
	Previous solid organ transplant or autoimmune disease	15	4%
	Not captured	26	7%

[d] Figures may not add to 100% due to rounding.

Treatment duration

Of the 352 patients with CDF applications, 207 (59%) were identified as having completed treatment by 30 April 2021 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with cemiplimab in at least three months (see Table 10). The median follow-up time in SACT was 5.5 months (167 days). The median treatment duration follow-up is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 22 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 23 months. SACT follow-up ends 30 April 2021.

Table 6: Breakdown by patients' treatment status[e, f, g]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	127	36%
Patient died – on treatment	18	5%
Treatment stopped	62	18%
Treatment ongoing	145	41%
Total	352	100%

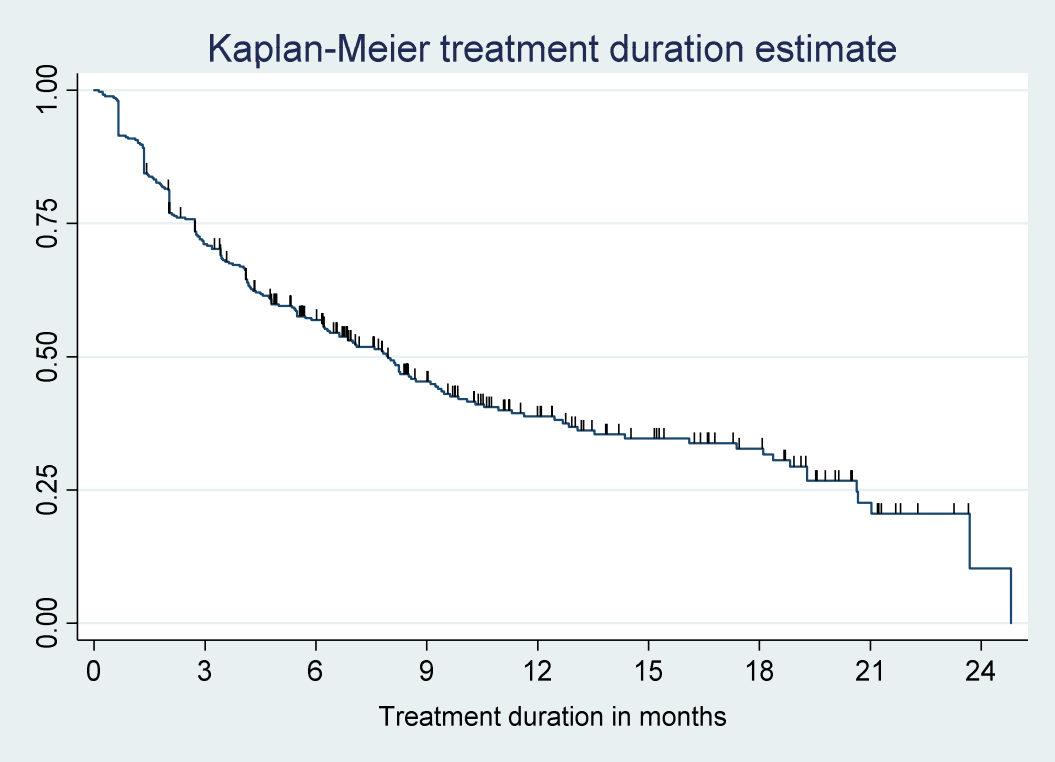
Table 7: Treatment duration at 6, 12- and 18-month intervals

Time period	Treatment duration (%)
6 months	57% [95% CI: 51%, 62%]
12 months	39% [95% CI: 33%, 44%]
18 months	33% [95% CI: 26%, 39%]

[e] Figures may not sum to 100% due to rounding.
[f] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[g] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 3. The median treatment duration for all patients was 8 months [95% CI: 6.2, 9.3] (243 days) (N=352).

Figure 3: Kaplan-Meier treatment duration (N=352)



Tables 8 and 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 21.9 months (666 days). SACT contains more follow-up for some patients.

Table 8: Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24	24
Number at risk	352	241	168	98	63	44	31	11	1

Table 9 shows that for all patients who received treatment, 145 were still on treatment (censored) at the date of follow-up and 207 had ended treatment (events).

Table 9: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24	24
Censored	145	135	108	67	45	32	21	8	0
Events	207	106	60	31	18	12	10	3	1

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 59% (N=207) of patients had ended treatment at 30 April 2021.

Table 10: Treatment outcomes for patients that have ended treatment (N=207)[h,i]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	49	24%
Stopped treatment – acute toxicity	19	9%
Stopped treatment – patient choice	9	4%
Stopped treatment – died not on treatmentj	34	16%
Stopped treatment – died on treatment	18	9%
Stopped treatment – completed as prescribed	6	3%
Stopped treatment – COVID	7	3%
Stopped treatment – palliative, patient did not benefit	21	10%
Stopped treatment – palliative, patient did benefit	35	17%
Stopped treatment – no treatment in at least 3 months	9	4%
Total	207	100%

[h] Figures may not sum to 100% due to rounding.
[i] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[j] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 11: Treatment outcomes and treatment status for patients that have ended treatment (N=207)

Outcome[k]	Patient died [l] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	35	14	
Stopped treatment – acute toxicity	12	7	
Stopped treatment – patient choice	2	7	
Stopped treatment – died not on treatment	34		
Stopped treatment – died on treatment			18
Stopped treatment – completed as prescribed	1	5	
Stopped treatment – COVID	2	5	
Stopped treatment – palliative, patient did not benefit	18	3	
Stopped treatment – palliative, patient did benefit	23	12	
Stopped treatment – no treatment in at least 3 months		9	
Total	127	62	18

[k] Relates to outcomes submitted by the trust in Table 10.

[l] Relates to treatment status in Table 6 for those that have ended treatment.

Overall survival (OS)

Of the 352 patients with a treatment record in SACT, the minimum follow-up was 6.3 months (191 days) from the last CDF application. Patients were traced for their vital status on 6 September 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 10.2 months (310 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 12: OS at 6, 12, 18 and 24-month intervals

Time period	OS (%)
6 months	75% [95% CI: 70%, 79%]
12 months	63% [95% CI: 58%, 68%]
18 months	56% [95% CI: 49%, 61%]
24 months	46% [95% CI: 37%, 54%]

Figure 4 provides the Kaplan-Meier curve for OS, censored at 6 September 2021. The median OS was 21 months[m] (639 days).

Figure 4: Kaplan-Meier survival plot (N=352)

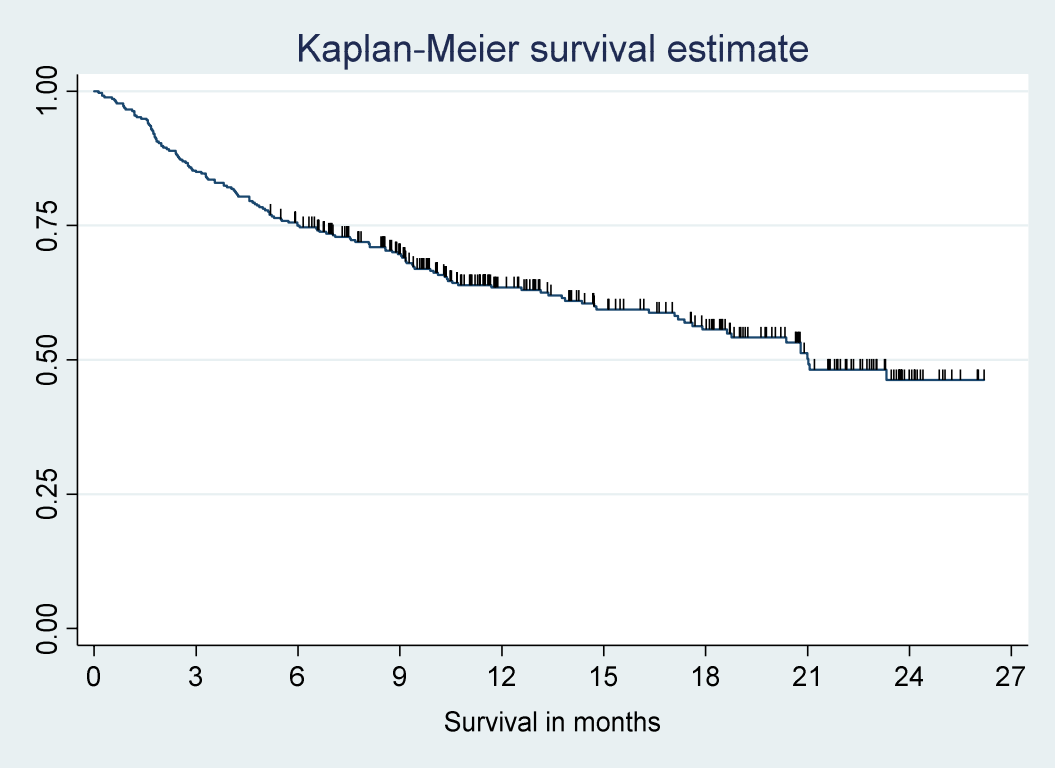


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 26.3 months (800 days), all patients were traced on 6 September 2021.

Table 13: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-27	3-27	6-27	9-27	12-27	15-27	18-27	21-27	24-27
Number at risk	352	299	259	207	141	107	85	49	12

Table 14 shows that for all patients who received treatment, 207 were still alive (censored) at the date of follow-up and 145 had died (events).

[m] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Table 14: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-27	3-27	6-27	9-27	12-27	15-27	18-27	21-27	24-27
Censored	207	207	202	167	118	92	76	46	12
Events	145	92	57	40	23	15	9	3	0

5. Sensitivity analyses

6-month SACT follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 2 July 2019 to 31 October 2020 and SACT activity was followed up to the 30 April 2021.

Following the exclusions above, 275 patients (78%) were identified for inclusion. The median follow-up time in SACT was 6.9 months (210 days). The median treatment duration follow-up is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 5. The median treatment duration for patients in this cohort was 7.8 months [95% CI: 6.2, 9.2] (237 days) (N=275).

Figure 5: Kaplan-Meier treatment duration plot (N=275)

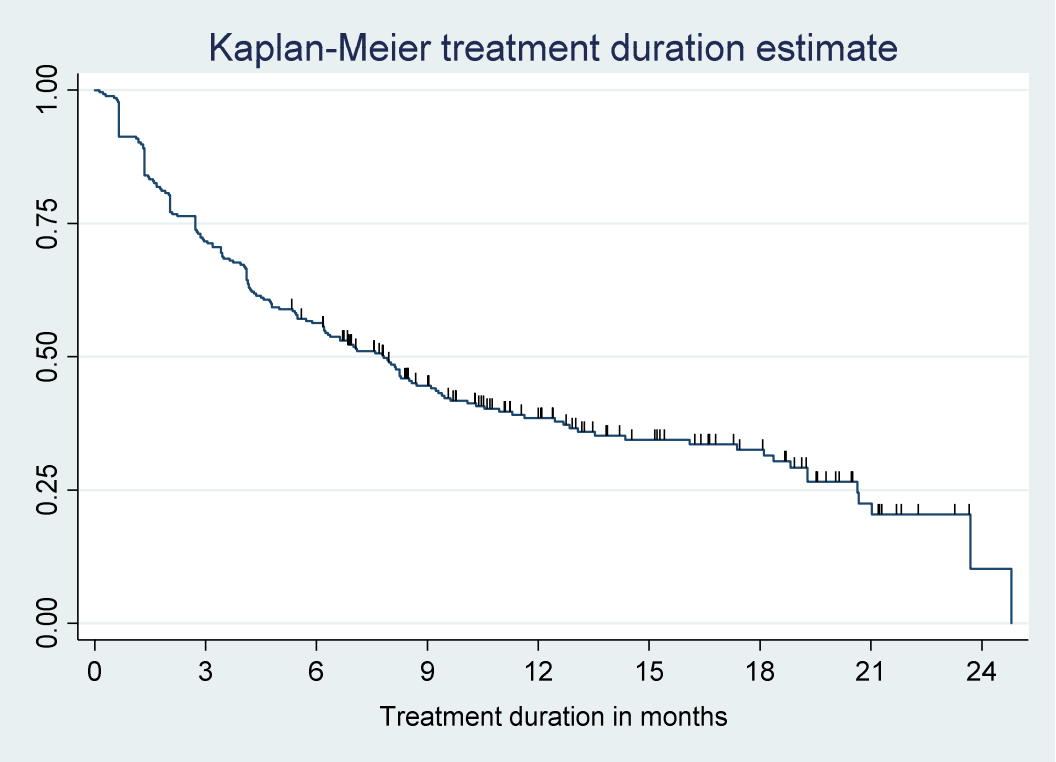


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time

patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 21.9 months (666 days).

Table 15: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24	24
Number at risk	275	197	153	96	63	44	31	11	1

Table 16 shows that for all patients who received treatment, 96 were still on treatment (censored) at the date of follow-up and 179 had ended treatment (events).

Table 16: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	21-24	24
Censored	96	96	94	66	45	32	21	8	0
Events	179	101	59	30	18	12	10	3	1

Table 17: Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration
N	352	275
Median treatment duration	8 months [95% CI: 6.2, 9.3] (243 days)	7.8 months [95% CI: 6.2, 9.2] (237 days)
OS	21 months[14] (639 days)	

[14] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

6.Conclusions

354 patients received cemiplimab for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma [TA592] through the CDF in the reporting period (2 July 2019 and 1 March 2021). 352 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99%. An additional three patients with a CDF application did not receive treatment and 12 patients died before treatment.

Patient characteristics from the SACT dataset show that 74% (N=262) of patients that received cemiplimab for metastatic or locally advanced cutaneous squamous cell carcinoma were male, 26% (N=90) of patients were female. Most of the cohort were aged 70 years and over 74% (N=262) and 82% (N=287) of patients had a performance status between 0 and 1 at the start of their regimen.

At data cut off, 59% (N=207) of patients were identified as no longer being on treatment. Of these 207 patients, 24% (N=49) of patients stopped treatment due to progression, 9% (N=19) of patients stopped treatment due to acute toxicity, 4% (N=9) of patients chose to end their treatment, 16% (N=34) of patients died not on treatment, 9% (N=18) of patients died on treatment, 3% (N=6) of patients completed treatment as prescribed, 3% (N=7) of patients stopped treatment due to COVID, 10% (N=21) of patients were treated palliatively and did not benefit from the treatment they received, 17% (N=35) of patients were treated palliatively and did benefit from the treatment they received and 4% (N=9) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration was 8 months [95% CI: 6.2, 9.3] (243 days). 57% of patients were still receiving treatment at 6 months [95% CI: 51%,62%], 39% of patients were still receiving treatment at 12 months [95% CI: 33%, 44%], 33% of patients were still receiving treatment at 18 months [95% CI: 26%, 39%].

The median OS was 21 months15 (639 days). OS at 6 months was 75% [95% CI: 70%, 79%], 12 months OS was 63% [95% CI: 58%, 68%], OS at 18 months was 56% [95% CI: 49%, 61%] and OS at 24 months was 46% [95% CI: 37%, 54%].

Sensitivity analysis was carried out on treatment duration to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for treatment duration

[15] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

showed a difference of 0.2 month (full cohort = 8 months; sensitivity analysis cohort = 7.8 months).

7. References

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Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review TA592)

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Neelam Kalita, Senior Research Fellow, Health Economics Lois Woods, Senior Research Assistant, Evidence synthesis and Information Specialist Joanne Lord, Professor, Health Economics Geoff Frampton, Senior Research Fellow, Evidence Synthesis
Correspondence to	Dr Geoff Frampton Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
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Declared competing interests of the authors

None

Declared competing interests of the clinical experts

Professor Healy is currently a collaborator in a study looking at genomic and transcriptomic factors that might associate with development of cutaneous squamous cell cancer metastases, funded by Sanofi (manufacturer of cemiplimab). Professor Healy declares that the only funds paid to the University of Southampton were costs of cutting tissue sections of Southampton samples. Dr Martin-Clavijo has received honoraria from Almirall (manufacturer of fluorouracil) for consultancy, chairing meetings and contributing to an educational steering committee in dermatology (primarily relating to inflammatory dermatosis) but has not been involved in any funded work on cutaneous squamous cell carcinoma or on fluorouracil. Dr Kate Fife received honoraria from Sanofi to present cases and experiences of patients who had received cemiplimab under the Cancer Drugs Fund, at a virtual meeting (February 2021); for training Sanofi employees in new national guidelines for squamous cell carcinoma (February 2021); to develop and present case studies for a virtual platform (April 2021); and to present patient cases and a summary of published trial data at an East of England Plastic Surgery Educational Meeting (September 2021). Dr Fife confirms that she did not participate in the company's cemiplimab trials, did not receive funding from the company specifically to work on cemiplimab, and did not contribute to the company's submission. Dr Fife also received honoraria from Pfizer (manufacturer of carboplatin, cisplatin and fluorouracil) for participating in a global advisory board (April 2021) which discussed renal cancer therapy.

Rider on responsibility for the report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Critique of the company's adherence to the committee's preferred assumptions from the Terms of Engagement

The company have largely adhered to the committee's preferred assumptions but there are some major limitations in the evidence base which limit how well the committee's assumptions can be addressed, as summarised below.

1.2 Summary of the key issues in the clinical effectiveness evidence

The company have submitted several new sources of evidence for cemiplimab, chemotherapy and best supportive care (summarised in section 2.3) and conducted indirect treatment comparisons (ITCs) on these (discussed in sections 3.1.6 and 3.1.7). Key issues relating to these evidence sources and comparisons are:

SACT dataset

- The SACT (Systemic Anticancer Therapy) dataset which the company provided as new evidence is reflective of current clinical practice and indicates that an older, frailer population than that of the company cemiplimab trials can be treated with cemiplimab in practice, albeit with lower overall survival. However, relatively limited population characteristics are available for the SACT dataset, and generalisability of the findings may be influenced by the COVID-19 pandemic. The company use the SACT data only in a limited way to validate outcomes of the cemiplimab trials, as they did not digitise the SACT overall survival KM data for comparison against results from the company's trials and modelled extrapolations.

Comparator studies

- Three retrospective comparator studies are included in the submission representing chemotherapy (company UK chart review – new evidence, Jarkowski study – existing evidence) and best supportive care (Sun study – new evidence). These all have major limitations, and the company themselves regard the chart review as having "poor face-

validity", meaning that despite the study being conducted in the UK the population characteristics and results are highly uncertain. The Jarkowski and Sun studies are both very small (N≤20) and were conducted in the USA, therefore of questionable reliability and relevance to UK clinical practice. The population characteristics and results of these studies are therefore also highly uncertain.

- These limitations mean that none of the included studies provide a reliable estimate of the effects of chemotherapy or of BSC in a UK setting. Thus, uncertainties in these comparators have not been reduced relative to the information that was available prior to the CDF appraisal in TA592.

Indirect treatment comparisons

- In the absence of any trials directly comparing cemiplimab against chemotherapy or best supportive care the company conducted several ITC analyses to enable these comparisons. However, the ITCs are all limited by the high uncertainty in the population characteristics and results of the comparator studies that they included.
- Additionally, the ITC methods are all subject to uncertainty due to the inability of ITC models to balance measured prognostic covariates and/or a lack of sufficient data to enable all measured prognostic covariates to be modelled.
- One of the ITC approaches comparing cemiplimab against chemotherapy estimated the average treatment effect in the treated group (ATT) and the average treatment effect in the comparator group (ATC) which provides an opportunity to select which study represents the target population of interest (i.e. the company trials according to the ATT approach, or the chart review according to the ATC approach). Poor face validity of the chart review study makes it unclear whether the chart review reflects a UK clinical practice population and hence whether an ATC model would be more appropriate than the company's preferred approach which uses an ATT model. However, all the tested ATT and ATC models failed to adequately balance the prognostic covariates so results of all the models are at high risk of confounding.
- Hazard ratios obtained from the ITCs require the proportional hazards assumption to be satisfied. This assumption does not hold for the ITCs comparing cemiplimab against chemotherapy and appears unlikely to hold for the comparison of cemiplimab against BSC. Hazard ratios therefore cannot be relied upon to assist interpretation of relative treatment effects from the ITC results.

Summary

Whilst the company have largely adhered to the Terms of Engagement, the new evidence from comparator studies provided for this CDF review has not reduced the uncertainty in the effectiveness of cemiplimab as used in the UK compared to platinum-based chemotherapy and BSC. The longer-term data available from the EMPOWER-CSCC 1 trial have limited value in establishing relative effectiveness of cemiplimab since comparable long-term data do not exist for the comparator studies.

The areas where uncertainty has been reduced are:

- Improved confidence in the stopping rule and improved follow up of survival outcomes in the trial setting as a result of longer-term data being available in the EMPOWER-CSCC 1 trial.
- The SACT dataset suggests that the company cemiplimab trials lack generalisability to UK clinical practice. However, the SACT dataset has limitations due to relatively few population characteristics collected, whilst the overlap between the SACT dataset and COVID-19 pandemic could influence generalisability of the SACT data.

1.3 Summary of the key issues in the cost effectiveness evidence

- Extended trial follow up has provided better evidence for the cemiplimab PFS and OS extrapolations than was available for the TA592 analysis. It also supports the assumption of longer maintenance of survival with cemiplimab, with data now available for a maximum follow up of 5 years. The company assume loss of the relative treatment effect (hazards equal to those of comparators) at 5 years, extended from 3 years in the TA592 analysis. The ERG consider this to be reasonable.
- However, the SACT dataset has demonstrated that the patients treated with cemiplimab in UK practice were on average older and less fit than those in the company's trials. This suggests that the OS and PFS extrapolations based on the trial data that are used in the company's base case are likely to be more favourable than one would expect in routine NHS practice.
- The indirect treatment comparisons between the cemiplimab trials and comparator studies (company chart review, Jarkowski study and Sun study) inform the OS and PFS extrapolations for chemotherapy and best supportive care. However, as noted above, the results of these ITCs are all highly uncertain, meaning that there is significant uncertainty over the comparability of the survival extrapolations for cemiplimab and the two comparators. In particular, the evidence used in the model

for best supportive care was very sparse (20 immunocompetent patients from the US, Sun study cohort).

- For progression free survival, the company rely on different sources to model OS and PFS for chemotherapy, and they assume that all patients on best supportive care start in the 'post-progression' health state.
- The company's approach to selecting distributions for the survival extrapolations appears reasonable. However, the rationale for the choice of the base case distribution for OS with chemotherapy (fitted to the chart review data) is not clearly explained. The company noted that distributions with a better fit to the chart review data had a plateau in long-term survival, which the company's advisory board did not consider plausible. Similarly for best supportive care, the company chose a log-logistic distribution for OS, fitted to the Sun study data. This was not the best-fitting distribution but was selected based on clinical opinion.

1.4 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted additional scenario analyses on the company's CDF model. The results of the company and ERG scenarios indicate that:

- The results are most sensitive to assumptions about: i) patient characteristics (age at treatment initiation); ii) waning of treatment effects; iii) OS & PFS extrapolations.
- Assumptions relating to efficacy and PFS adjustment also influenced the cost-effectiveness results, but to a lesser extent.
- The ICERs for the comparison with chemotherapy ranged between £33,195 (Gompertz distribution for PFS with chemotherapy) and £43,233 (Treatment waning at 42 months). For the comparison with best supportive care, the ICER ranged between £32,646 (mean age at baseline of 81 years, 80% male, based on the population in an Italian cemiplimab cohort[7]) and £28,859 (no population adjustment of indirect comparison).

Note that these scenarios do not capture the more fundamental uncertainties arising from the limitations of the comparative evidence described above.

1.5 Summary of ERG's preferred assumptions and resulting ICERs

We prefer the scenario based on the demographics of the SACT cohort, as this reflect the population treated with cemiplimab in UK NHS practice, see Table 1 below. This increases the ICER of cemiplimab versus chemotherapy by £1,612 (from the company's base case

ICER of £36,163 to £37,775) and that of cemiplimab versus BSC by £1,514 (from £29,438 in the company's base case to £30,952).

Table 1 ERG preferred assumption (PAS price)

Assumption	ICER vs PBC	ICER vs BSC
Company base case	£36,163	£29,438
+ Population characteristics from SACT database (age: 77 years; 74% male)	£37,775	£30,952
ERG preferred assumption	£37,775	£30,952
Abbreviations: BSC best supportive care; PBC platinum-based chemotherapy; O; ICER incremental cost-effectiveness ratio; PAS patient access scheme		

A range of scenarios was conducted on the ERG preferred assumption, which included varying assumptions on:

- Time to waning of treatment effects (e.g. at 4 years, and between 5 and 8 years)
- Using different models for population adjustment in the ITCs
- Extrapolating survival for cemiplimab and the comparators using different distributions (e.g. Weibull, Second order P(0,-1), Loglogistic, Gompertz, Lognormal)
- Adjusting the method for estimating PFS for the comparators (based on the relationship between PFS and OS in the Jarkowski cohort).

ERG scenarios around these assumptions showed that:

- The ICER for cemiplimab versus chemotherapy ranged between £44,379 and £33,942 and between £33,246 and £30,793 comparing cemiplimab versus BSC.
- The cost-effectiveness results are most sensitive to assumptions about OS extrapolations, treatment waning, and adjusting the PFS for the comparator arms.
- However, these analyses do not capture the underlying uncertainties related to generalisability of the trial data and weaknesses in the evidence base for the indirect comparisons.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to the NICE Cancer Drugs Fund (CDF) review of TA592 on the clinical effectiveness and cost effectiveness of cemiplimab for treating cutaneous squamous cell carcinoma. Clarification on some aspects of the CS was requested on 24th January 2022. The company's response was received by the ERG on 4th February 2022 and a corrected version of the company's economic model was received on 8th February 2022.

The CS accurately reports the recommended use of cemiplimab within the CDF (CS section A1) and the licensed indication (CS section A4).

2.2 Background

Cemiplimab (Libtayo®) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed death 1 (PD-1) receptor. It was granted a conditional marketing authorisation in July 2019 and a full marketing authorisation is anticipated in [redacted]. Cemiplimab is indicated as a monotherapy for adults with locally advanced or metastatic cutaneous squamous cell carcinoma (laCSCC or mCSCC) who are not candidates for curative surgery or curative radiation. The company acknowledge that the licensed dose according to the Summary of Product Characteristics is 350mg every three weeks via intravenous infusion over 30 minutes. Treatment with cemiplimab may be continued until disease progression or unacceptable toxicity. We note that the pivotal studies applied a stopping rule of 22 months, disease progression or death, whichever is sooner (CS section A.6.1.2).

In the original appraisal (TA592), NICE recommended cemiplimab for use within the Cancer Drugs Fund (CDF) according to the licensed indication and conditions in the Managed Access Agreement. The recommendation includes a 24-month stopping rule. TA592 concluded that the cemiplimab trial data were promising but uncertain. The data were considered immature as median overall survival had not been reached. The cost-effectiveness estimates were above what is normally considered a cost-effective use of NHS resources. Additionally, there was little evidence available on life expectancy with current treatments for advanced CSCC making it uncertain how long cemiplimab might prolong life and whether the end-of-life criteria apply. More mature data and more data on life

expectancy with current treatments may confirm the expectation that end-of-life criteria apply and that cemiplimab may be a cost-effective treatment.

In the previous appraisal TA592 the company's evidence for cemiplimab was obtained from the phase II EMPOWER CSCC-1 study (N=193) and the phase I study 1423 (N=26) which were pooled to give a single cohort (N=219). The TA592 NICE Committee agreed with the combining of these studies into a single cohort. In the current CDF review the company have also combined the two cemiplimab studies into one cohort. For brevity we refer to this pooled cohort throughout this report as the "company trials".

The relevant comparators in the current CDF review are chemotherapy and best supportive care (BSC). The company have limited their interpretation of chemotherapy specifically to mean platinum-based chemotherapy which is consistent with their submission in TA592. BSC is not clearly defined in oncological literature generally[1 2] and the CS states it is "where treatment options are palliative" (CS section A.6). For the purposes of this review we understand BSC to mean any treatment or care that is for managing symptoms and is without curative intent.

2.3 New evidence

The company's CDF review submission provides new evidence for clinical effectiveness from several sources. New evidence for cemiplimab is summarised in Table 2 below and discussed further in sections 3.1.2 and 3.1.3. New evidence for the comparators is listed below and discussed further in sections 3.1.5.1 and 3.1.5.3.

New evidence for the comparators:

1. **Company chart review:** a retrospective study of patient records conducted on behalf of the company by a third party provides OS evidence for platinum-based chemotherapy (PBC) for advanced CSCC in a UK population. Discussed in section 3.1.5.1 of this report.
2. **Sun et al. 2019 study** [3] a retrospective study of patient records identified by the ERG during the technical engagement phase of TA592 provides OS evidence for best supportive care (BSC). Discussed in section 3.1.5.3 of this report.

Table 2 New evidence for cemiplimab

Study		**Phase I Study (Study 1423) N=26**	**Phase II EMPOWER-CSCC 1 (Study 1540) N=193**	**Systemic Anti-Cancer Therapy (SACT) dataset N=352**
Overview		Additional data from a more recent data cut of the company phase I multicentre safety study	Additional data from a more recent data cut of the company phase II non-randomised, non-comparative, three-group multicentre study	Real-world data collected by Public Health England (PHE)/NHS Digital on UK patients treated with cemiplimab within the CDF during the two-year Managed Access Agreement period
Median follow-up, months (range)	**CDF review**	31.7 (1.1 to 47.0)	[redacted]	10.2 (6.3 to 26.3)
	TA592	11.1 (1.1 to 17.0)	8.6 (0.8 to 15.9)	Not applicable
Dosing [a]	**CDF review**	(n=26): weight-based dose (laCSCC & mCSCC)	Group 1 (n=59): weight-based dose (mCSCC) Group 2 (n=78): weight-based dose (laCSCC) Group 3 (n=56): flat dose (mCSCC) New evidence includes data from 56 new patients (23 in Group 2 and 33 in Group 3).	Not explicitly reported. The SACT Report refers to a 3-week treatment cycle which corresponds with the flat dose regimen.
	TA592	(n=26): weight-based dose (laCSCC & mCSCC)	Group 1 (n=59): weight-based dose (mCSCC) Group 2 (n=55): weight-based dose (laCSCC) Group 3 (n=23): flat dose (mCSCC)	Not applicable

Outcomes and data cuts (data in bold inform the economic analysis)	**CDF review**	**OS (2019)** [b] **PFS (2019)** [b] **Safety** Overall response rate Duration of response	**OS (July 2021)** **PFS (IRC assessed, July 2021)** **Safety (October 2020)** [c] **HRQoL (October 2020)** Overall response rate Duration of response Treatment duration	OS Treatment duration **Patient characteristics** (scenario analysis only)
	TA592	OS (October 2017) PFS (October 2017)	OS (October 2017) HRQoL (October 2017)	Not applicable
Pooled data provided by the company	**CDF review**	Combined results from both studies form a single cohort (N=219) referred to in this report as 'the company trials'.		Not applicable
	TA592	Combined results from both studies formed a single cohort (N=163)		

[a] Weight based dose: 3mg/kg IV every 2 weeks; flat dose: 350mg IV every 3 weeks.
[b] The company confirmed at the clarification meeting that the 2019 data cut was used for the analysis in this review (CS Table 3 erroneously reports a 2021 data cut)
[c] CS Table 3 says July 2021 but clarification question A28 says October 2020.
CDF: Cancer Drugs Fund; HRQoL: Health Related Quality of Life; IRC: independent review committee; IV: intravenous infusion; OS: overall survival; PFS: progression-free survival.
Sources: CS Table 3, CS section A.6.5, SACT Report, Clarification questions response, TA592 company submission.

2.4 Critique of the company's adherence to the Terms of Engagement

The ERG's critique of the company's adherence to the Terms of Engagement (ToE) is shown in Appendix 1 and a summary is provided in Table 3 below. Overall, the company have addressed the NICE Committee's preferred assumptions as stated in the ToE. However, the evidence for relative effectiveness of cemiplimab compared against chemotherapy and best supportive care remains highly uncertain, primarily because of methodological limitations with the comparator studies (discussed in sections 3.1.5.1 to 3.1.5.3 below) which produce uncertainty in the results of the indirect treatment comparisons (section 3.1.7 below). The company have considered SACT data in their submission but do not explicitly use the SACT results to validate survival extrapolations. Whilst the SACT data inform an economic scenario analysis, this only reflects the impact of SACT cohort demographics (age and gender) on general population mortality rates and utilities (section 4.2 below). SACT data reflect patients treated with cemiplimab during the COVID-19 pandemic which could influence generalisability of the SACT results (section 3.1.3 below).

Table 3 Summary of the company's adherence to the Terms of Engagement (ToE)

Terms of Engagement item	Addressed by company	ERG comments (for details see Appendix 1)
Population	Yes	The company have addressed the ToE, but there are uncertainties regarding data validity in the company's chart review.
Comparators	Yes	Note that chemotherapy is limited to platinum-based, which is consistent with TA592.
Generalisability of trial evidence	Yes, with limitations	The company have considered the SACT data. This indicated differences between the population treated with cemiplimab in NHS practice and the trial populations, although these data were collected during the COVID-19 pandemic which would likely influence generalisability.
Survival outcomes	Partly	Survival extrapolations based on updated trial data were explored but were not informed by data from the SACT dataset.
Comparator data	Yes, with limitations	The company have addressed the ToE, but the results of all comparator studies are uncertain due to methodological limitations.

Relative effectiveness	Yes, with limitations	The company have addressed the ToE, but results of all indirect treatment comparisons are uncertain because of the uncertainty in the comparator studies and the indirect comparison methods.
Treatment effect duration	Yes	The company have addressed the ToE: they have used the updated survival data from EMPOWER-CSCC 1 and explored the impact of a 24-month stopping rule on long-term outcomes.
End of life	Yes	The company argue that cemiplimab meets end-of-life criteria compared to both chemotherapy and BSC. However, their base case model indicates that the criteria are met for the comparison with BSC, but not for the comparison with chemotherapy (as the life expectancy exceeds 2 years). The ERG preferred scenario reiterates this conclusion. Overall, it remains unclear if cemiplimab meets end-of-life criteria due to high uncertainty in the comparator data. This issue warrants further discussion with clinical experts.

3 CLINICAL EFFECTIVENESS

3.1 Critique of new clinical evidence

3.1.1 Updated systematic review of clinical effectiveness evidence

The company performed an updated systematic literature review (SLR) on 17th July 2021 (CS section A.15.16), but the CS does not provide details. The company identified one potential additional study on cemiplimab[6] but excluded it for several reasons, including it being a non-UK study and having relatively high proportions of immunocompromised patients (24%) and those with ECOG PS ≥2 (27%). The ERG agree with the exclusion of this study.

Given the lack of details about the company's updated SLR, the ERG conducted a search to check whether any evidence might have been missed. We searched MEDLINE and Embase using the company's search strategies from the original TA592 submission without the study design filters and using date limits to cover the period since the latest search in November 2018. We found nine retrospective real-world studies for an advanced CSCC population including the French study identified by the company (Appendix 2). All were non-UK studies and we concluded that none of these would be eligible for inclusion in this CDF review, primarily because most studies did not report either OS or PFS, or because outcomes were not reported for population subgroups relevant to this review.

Details of the company's updated SLR were subsequently provided in a separate Systematic Review Technical Report (clarification response A1). The company carried out thorough searches for studies that assessed the efficacy of cemiplimab and all alternative interventions (not only PBC or BSC) for treatment of patients with advanced CSCC. They identified 42 new citations bringing the total number in their review to 66 citations representing 50 studies. Appendices B-E in the company SLR Report clearly detail study characteristics, patient characteristics and outcomes of the included studies and the ERG did not identify further studies relevant to this CDF review from them. We are satisfied that all relevant available published evidence is included in the review.

Following the literature searches described above, one of the ERG's clinical experts identified a recent conference abstract reporting a retrospective study of UK patients in the

UK Named Patient Scheme who had received cemiplimab before it was funded via the CDF.[9] We understand that the full paper has been submitted for publication. Information available in the study abstract is summarised in section 3.1.4 below.

3.1.2 Company trials

Overview

The strengths and limitations of the company trials were discussed in the original appraisal (see TA592 ERG report sections 3.1.3 to 3.1.6). The main concerns were that they were non-comparative and had relatively short follow-up with immature data. The new evidence included in this review is summarised in Table 2 above. It shows that the median follow-up has increased by 35.1 months (from [redacted] to [redacted] months) with a maximum follow-up of [redacted] months. Fifty-six additional patients were recruited to the phase II trial, increasing the pooled cohort to 219 patients.

Generalisability of the dosing regimens

The cemiplimab phase II trial contains three subgroups of patients (CS Table 5):
Groups 1 and 2 received the weight-based dose (3mg/kg IV every 2 weeks, total 137 patients) and group 3 received the flat dose which is the licensed indication (350/mg IV every 3 weeks, total 56 patients). CS section A.6.1.1 states that the results remain consistent between the three groups despite the different dosing regimens, but no evidence was presented for the ERG to verify this. In clarification response A2 the company provided objective response rates and KM curves for OS and PFS for each group from an October 2020 data cut because formal analyses of these subgroups were not yet available for the July 2021 data cut (the company have requested these but it is unclear whether they will be available within the timeframe of this CDF review). These data are relatively limited, without hazard ratios and confidence intervals for the survival data provided. However, we agree the results appear broadly consistent across the weight-based and flat dose groups.

Results

OS data are still immature (median survival has still not been reached) with the survival rate reported as [redacted] at a median follow up of [redacted] (maximum [redacted]) months (CS section A.6.1.2). The increased follow up is sufficient to analyse a 24-month stopping rule as specified in the Terms of Engagement. Median PFS was [redacted] (CS section A.6.1.3).

ERG conclusion

The company trials are the main source of cemiplimab treatment data used to inform the economic model in this CDF review. The additional data provide longer follow-up with a modest increase in the sample size. The new data, although limited, suggest that weight-based and flat cemiplimab doses have similar effects on OS, although information from the latest data cut would be desirable to confirm this.

3.1.3 SACT dataset

Overview

The SACT (Systematic Anti-Cancer Therapy) dataset is a cohort of 352 patients who received cemiplimab under the CDF from July 2019 to April 2021. It has a median follow-up of 10.2 months (range 6.3 to 26.3 months) for OS and 5.5 months (maximum 21.9 months) for treatment duration both of which are much shorter than the median follow-up for the company trials. The SACT dataset is reported in CS section A.6.5 and in a Public Health England report [4] (hereafter referred to as the SACT Report) that was provided in clarification response A3.

Eligibility criteria

Eligibility criteria in the SACT Report are consistent with those in the Managed Access Agreement.[10] There were 393 CDF applications during the review period and 41 were excluded (8 duplicate applications; 16 who received cemiplimab prior to the CDF; 12 died before treatment; 3 did not receive treatment; 2 were missing). The company did not apply any additional eligibility criteria to the SACT dataset. No reasons are given for why three people did not receive cemiplimab; one of the ERG's clinical experts suggested this may have been due to clinical deterioration. The SACT Report does not say whether any patients received cemiplimab other than as intended.

The Managed Access Agreement specifies an ECOG performance status of 0-1 in order to receive treatment with cemiplimab. However, 4% of patients in the SACT dataset had a status of ECOG PS 2 and 14% had no status recorded meaning up to 18% of patients might have had a performance status greater than 1 (we note that other recent real-world studies reported that between 20% and 27% of patients with an ECOG performance status greater than 1 had received cemiplimab, although none of these were UK studies[5-8]). Patient eligibility in the Managed Access Agreement allows for cemiplimab to be used with caution in immunosuppressed patients, and only 4% of patients in the SACT dataset were immunocompromised (SACT Report Table 5). Reasons for missing data for ECOG

performance status (14%) and (7%) are not provided so it is unclear whether these may have been related to the therapy or outcome.

Population characteristics

A limited set of population characteristics were collected for the SACT dataset: disease severity (laCSCC or mCSCC), median age, gender, and ECOG performance status. Median age was 77 years, compared to 72 years in the company trials. SACT also represents an older population than those of the comparator studies (Appendix 3). Based on the limited data available, the ERG's clinical experts considered the SACT dataset to be a good reflection of UK clinical practice and noted that the population could be considered frailer than that of company trials (NB the experts referred to frailty in a general sense, mainly reflecting the older population age; instruments that specifically assess frailty were not reported in the studies).

Influence of the COVID-19 pandemic

The company acknowledge (CS section A.6.5) that the COVID-19 pandemic, which started eight months after cemiplimab entry into the CDF, may have affected treatment with cemiplimab, and hence the SACT dataset. The ERG's clinical experts suggested the pandemic would have caused service disruption for several reasons, including delayed referrals when patients were unable to access GPs or other clinicians and the cancellation of all surgery, precluding patients who were candidates for surgery from receiving it. The pandemic would likely have impacted on clinical assessments, treatment options and outcomes, and there may have been extended dosing intervals or missed doses of cemiplimab. Contributory factors include staffing shortages in infusion centres, lack of transport to hospital if relatives/drivers were infected, fear of catching COVID-19 at the hospital or in transport, and clinician uncertainty about the effect of COVID-19 on CSCC patients, such as the risk of autoimmune side effects. The ERG's clinical experts suggested that during the pandemic patients presented with more advanced disease and progressed more, with one expert observing that the proportion of patients with laCSCC increased.

Generalisability of SACT

The company argue in CS section A.6.5 that patients in the SACT dataset may have had poorer PS than recorded, which we agree is plausible, albeit speculative. The company's and ERG's clinical experts concur that cemiplimab is used to treat an older population than that included in the company trials, although the ERG's clinical experts noted that cemiplimab may be less effective in older patients. The company consider that as the SACT

cohort has shorter follow up than the company trials, longer trial data would be preferable (CS section A.6.5). However, we note that median OS was reached in the SACT cohort and the value of the cohort (and its purpose as stated in the Terms of Engagement) is to reflect UK clinical practice rather than a trial setting. The company explored the impact of the SACT population characteristics (age and gender) as a scenario analysis in their economic model (CS section A.12).

Results

OS was defined as starting from treatment initiation in both the SACT dataset and the company trials. Median follow up for OS was 10.2 months (range 6.3 to 26.3 months) compared to [redacted] in the company trials. OS was 63% at 12 months, 56% at 18 months and 46% at 24 months which is lower than in the company trials. Median OS was 21 months (Table 4) whereas median OS was not reached in either of the company trials. The company argue that an older and frailer population in the SACT dataset may be an explanation for reaching median OS sooner. The ERG also note that the COVID-19 pandemic may have impacted negatively on OS, and some patients could have died of other causes, e.g. COVID-19.

Treatment duration in the SACT dataset was defined as the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length. Median treatment duration for all patients was 8 months (95% CI 6.2 to 9.3 months).

Table 4 Survival estimates in the cemiplimab and comparator studies

Study	Median OS	Median PFS
Company trials (cemiplimab) (July 2021 data cut)	Median OS not reached. [redacted] OS at a median of [redacted] months (maximum [redacted] months) follow up. (CS section A.6.1.2)	[redacted] in the phase II trial (CS section A.6.1.3) [a]
SACT dataset (cemiplimab)	21 months [4] [b]	Not reported
Company chart review (chemotherapy)	[redacted] months" (CS section A.6.2.2) [b]	Not reported
Jarkowski study (chemotherapy)	15.1 months [11] [b]	9.8 months [11] [b]
Sun study (best supportive care)	5.0 months [3] (95% CI 2.6 to 14.4 months)	Not reported
CI: confidence interval		

[a] CS section A.6.1.3 reports median PFS as 18.4 months for the pooled studies whereas CS Table 7 reports median PFS as 22 months for each individual study. The reason for this discrepancy is unclear.
[b] Range and confidence interval not reported

ERG conclusion

The SACT dataset is representative of a UK population receiving treatment for advanced CSCC with cemiplimab, confirmed by expert clinical opinion. Patients in the SACT dataset are older, possibly frailer, than those of the company trials, reflecting that an older population can receive cemiplimab in clinical practice. Follow up in SACT was shorter than in the company trials, but median OS was reached (21 months). OS in the SACT population is lower than that of the company trials, likely reflecting the older (perhaps frailer) population and impact of the COVID-19 pandemic, although the extent to which these factors influenced OS is uncertain, since only four population characteristics are reported, limiting detailed interpretation.

3.1.4 Named Patient Scheme study

This study[9] was identified by the ERG (section 3.1.1) but not included in the CS. A summary of the information available in the abstract is provided here as the study is relevant to the scope of this CDF review. The full paper has been submitted for publication.

This was a retrospective study[9] of UK patients in the Named Patient Scheme who received cemiplimab for laCSCC or mCSCC prior to CDF funding. Forty-seven patients were enrolled across 17 centres. Nine patients progressed and were deemed unfit for treatment prior to starting cemiplimab, leaving a total study population of 38. Patients enrolled from November 2018 to July 2019 and the data cut is May 2020, with a median of 8 (range 1-24) treatment cycles and 8.7 (range 0.3 to 16.1) months of follow up. Patients were younger (median age 74 years) than those in the SACT dataset (median 77 years), a greater proportion of patients had metastatic or nodal disease, or both (Appendix 3) and 3/38 (8%) were immunocompromised. Median OS was 12.6 months (compared to 21 months in the SACT dataset); 60.5% of patients were alive at one year; median PFS was 7.7 months; and 34.2% of patients were continuing on cemiplimab at data cut off. The abstract reports that survival outcomes were significantly affected by disease stage and not by age, performance status or line of treatment.

ERG conclusion

The Named Patient Scheme study provides relevant context for the use of cemiplimab in a

UK clinical setting. However, limitations are that it is a small, retrospective study with a very short follow-up period, and only conference abstract details are currently available.

3.1.5 Comparator studies

Three studies were identified by the company as providing relevant comparators (i.e. chemotherapy or best supportive care for people with advanced CSCC. These are all retrospective chart reviews. The ERG and our clinical experts agree that these studies represent the most relevant available comparator data for the decision problem. Other related advanced CSCC cohort studies exist but are either not generalisable to UK practice or have other limitations (Appendix 2).

3.1.5.1 Company chart review: chemotherapy (OS)

Eligibility criteria

The company provided a protocol for their retrospective chart review (clarification response A9[a]). Eligibility criteria for the chart review are reported in section 3.1.2.1 of the Chart Review Report[12] and are consistent with those stated in the protocol. The eligibility criteria aimed to obtain a population of patient records with characteristics comparable to those of people enrolled in the company trials. We note two differences between the eligibility criteria of the chart review and those of the company trials:

- The proportions of laCSCC and mCSCC patients was not specified as an eligibility criterion for the company trials but a 60:40 balance of mCSCC to laCSCC patients was specified for the chart review (protocol page 9). The final ratio of mCSCC to laCSCC patients reported for the chart review (CS Table 23) therefore may not reflect the ratio of these groups seen in clinical practice.
- The chart review eligibility criteria do not specify any limits on the ECOG performance status of patients whereas those enrolled in the company trials had ECOG PS ≤1.

Data collection

To allow for potential (retrospectively observed) follow up of at least 24 months the chart review included patients whose diagnosis of laCSCC or mCSCC fell between 1st January 2011 and 31st December 2015. For the purposes of this appraisal the analysis was restricted to UK patients (N=106, from 25 centres). The data collection was contracted to a third-party

vendor, Medical Data Analytics (MDA) and the company had no direct contact with the study sites or de-identified patient data (clarification response A11).

After initial data collection the company raised concerns that several aspects of the data "did not align with clinical expectation" and were not fully comparable to the company trials (CS section A.15.6; section 3.1.2.2 and Appendix A in the Chart Review Report). The ERG critiqued the company's concerns, and our clinical experts commented that incomplete and ambiguous reporting of key information limits the usefulness of the chart review and impedes interpretation of the results (see Appendix 4).

The company provided the original MDA data collection forms in response to clarification question A7. However, the forms do not confirm whether investigators were expected to complete all fields in the forms, nor which IPD were finally collected. The IPD were not provided to the ERG, so we are unable to check validity of the summary results presented in the CS and Chart Review Report.[12]

Chart review audit

The company state that "*on the advice of clinical experts an audit of the UK cohort was conducted to investigate data quality*". Detailed methods of the audit (e.g. whether it was based on a protocol, and how many investigators collected and checked data) are not provided in the CS. The Chart Review Report[12] states that additional data elements were collected which included the reason why a patient was unresectable, confirmation of the date of metastatic disease, location of metastases, baseline biopsy date and location, confirmation of additional biopsies, and reasons for radiation at baseline. The audit aimed to clarify why laCSCC patients were deemed not to be candidates for surgery or radiation and why these patients had extended survival compared to other published estimates in the same population (Chart Review Report Appendix A1).

Site participation in the audit (which occurred during the COVID-19 pandemic) was voluntary. Of the original population, [redacted]/106 patients from [redacted]/25 of the centres were audited. The company integrated the data from these [redacted] audited patients into the original data set (i.e. N=106) to create "*enriched profiles*" of patients whose records were audited (CS section A.6.2.1). The company explain in clarification response A8 that "enriched profiles" were those in which the data points changed between the original chart review, and the original chart review data were replaced with the audit data as these were anticipated to be more accurate. The ERG requested clarification on which data points had changed

following the audit but the company's explanation is not specific: "*Additional data points around excisional biopsies, surgeries, radiotherapy, and systemic treatments both before and after their advanced CSCC diagnosis*" (clarification response A7).

Post-hoc eligibility criteria applied after audit

Following the audit the company observed residual differences between the chart review population and that of the company trials. They applied three further post hoc decision rules to identify those patients who received treatment in real-world clinical practice who would have been eligible for treatment with cemiplimab in the company trials. These decision rules are shown in CS Figure 3 and summarised in Table 5 below. These rules led to the exclusion of [redacted]/106 patients, leaving [redacted] patients (of which [redacted] were audited) in the final chart review analysis population.

Table 5 Post hoc decision rules for excluding patients from the chart review

Rule	Company exclusion rationale	ERG comments
1	[redacted]	The company's reasons for excluding these [redacted] patients appear broadly reasonable, but the ERG are unable to check consistency of the cited data since only summary statements of the IPD are provided. The ERG are unclear whether the [redacted] patients described would all have been eligible for BSC, since Chart Review Report section 3.1.2.2 states that for two of these patients the intent of radiotherapy was recorded as curative, whilst for some other patients the intent was not recorded.
2	[redacted]	The ERG and our clinical experts agree that these exclusions are appropriate as they are consistent with the eligibility criteria for the company trials.
3	[redacted]	

Baseline characteristics of the final analysis population ([redacted]) and the set of audited patient records ([redacted]) (Chart Review Report Table A1) suggest that the audited subset, despite

not being a random sample, is broadly reflective of the characteristics of the final analysis population. OS KM curves are reported for the [redacted] chart review patients, [redacted] chart review patients "enriched" with audit data for [redacted] of them, and for the [redacted] audited patients alone in Chart Review Figure A5. These curves mostly overlap, suggesting that these groups had similar OS.

Chart Review Report Appendix A1 states that the audit provided some clarification on the significant treatment data gaps for some patients but "*did not provide any additional clarification on the absence of PFS events or absence of prior treatments, whilst also raising questions about validity of reporting on treatment duration in the population*." The ERG note that higher than expected survival estimates observed for patients receiving systemic therapy (CS section A.15.6) were resolved following the audit process; however, the other face validity concerns were not resolved by the audit process (Appendix 4). Results reported for the chart review (see below) therefore remain uncertain.

Company and ERG assessments of study validity

The company and ERG did not conduct separate risk of bias assessments on the chart review using any published risk of bias tools. Limitations to the validity of the chart review study have been extensively discussed by the company and ERG as stated above and we deemed it unlikely that an additional assessment of the risk of bias would add new information, given that several key threats to validity were identified. These include: a risk of selection bias due to the retrospective data collection and application of post-hoc decision criteria; unavailability of the source IPD precluding validation of data by the ERG; and considerable uncertainty in the study methods due to lack of clarity in reporting.

The company acknowledge that following initial data collection there may have been patient selection bias (Chart Review Report Appendix A1). The company provided an extract of the study protocol, stating the intended process for checking data (clarification response A11), but did not provide information on the degree of protocol adherence or deviations, or on the number of reviewers who checked data or the rate of errors identified, either in the initial data collection or in the chart review audit.

Results of the chart review

Baseline characteristics of the chart review cohort post-audit [redacted]) are provided in Appendix 3 (this is an ERG- corrected version of CS Table 23). As the chart review eligibility criteria aimed to provide a cohort with baseline characteristics similar to those of the

company trials it would be expected that the chart review characteristics would be closer to those of the company trials than to those of the SACT dataset. This is true for median age (70 years compared to 72 years in the company trials and 77 years in SACT). But the chart review included a smaller proportion of patients with ECOG PS=0 ([redacted]) than the SACT dataset (18%) and company trials (45%). The chart review also included fewer patients than the company trials who had prior systemic therapy ([redacted] versus 34%) or prior radiotherapy ([redacted] versus 68%) but a greater proportion with undifferentiated tumours ([redacted] versus 66%) and T3-T4 stage tumours ([redacted] versus 32%) (SACT data are unavailable for these characteristics) (Appendix 3). We conclude that there is heterogeneity in baseline characteristics between the chart review and the company trials although it is unclear whether this is clinically meaningful given the issues with data reliability in the chart review discussed above and in Appendix 4.

CS Figure 68 compares the OS KM curve from the chart review (post-audit, [redacted]) against KM curves from the other studies that were included in the CDF review. Corresponding median OS estimates are summarised in Table 4 above. The median OS in the chart review is reported imprecisely as "~15 months", without confidence intervals. The company do not report median PFS since PFS events were not reliably recorded (Appendix 4). OS in the chart review is similar to that seen in the Jarkowski chemotherapy study (CS Figure 68 and Table 4 above). However, as with the baseline characteristics these chart review results are uncertain because of the key issues with face validity of the chart review.

ERG conclusion

The company have excluded BSC patients from the chart review and were unable to estimate PFS, meaning that the chart review serves as a comparator study for OS on platinum-based chemotherapy only. The exclusion of BSC patients and of the PFS outcome appear broadly appropriate but IPD were not provided and so the ERG have not been able to verify the summary data reported in the CS and Chart Review Report.[12] The company's chart review suffers from multiple issues of face validity, as acknowledged by the company and ERG's clinical experts, and results are at high risk of selection bias due to the retrospective data collection and post hoc application of eligibility criteria.

3.1.5.2 Jarkowski study: chemotherapy (OS and PFS)

Methods

This was a retrospective chart review of patients diagnosed with CSCC from January 2001 to January 2011 in the United States.[11] The study included 25 patients, of whom only 18 had

received relevant platinum-based chemotherapy and are relevant to the current appraisal. In their original CS for TA592 the company noted that treatment characteristics, such as dose and schedule, were not reported in the study so the company assume that the doses and schedules of systemic treatments in Jarkowski et al. 2016 were similar to those of other CSCC studies or clinical trials conducted in head and neck squamous cell carcinoma populations (TA592 CS Appendix D.1.3.2).

Company and ERG assessments of study validity

The company and ERG assessments of study validity are provided in section 3.1.4 of the TA592 ERG report. The ERG noted that although this study had an adequate duration of follow-up, it is very small (N=18) and at high risk of bias due to the retrospective selection of cases. In addition, the generalisability is unclear due to having a non-UK population, younger age, and higher proportion of trunk lesions than would be expected in NHS clinical practice, as well as limited reporting of baseline characteristics.

Results

Results of the study have been reported and discussed in the CS and ERG report for TA592 and remain unchanged. Patients in the Jarkowski study had a lower median age (66 years) than those in the company chemotherapy chart review (70 years) and company cemiplimab trials (72 years) but it is difficult to compare the studies on other characteristics due to the limited information reported and because locoregional and metastatic are not defined in the Jarkowski study and do not appear to equate to laCSCC and mCSCC as defined by the company (Appendix 3). Results of the ITCs including the Jarkowski study are reported in section 3.1.7 below.

ERG conclusion

Despite having major limitations, the Jarkowski study is the most relevant source of platinum-based chemotherapy data to inform the PFS outcome for this appraisal (company base case). The company also include OS data from the Jarkowski study in a scenario analysis.

3.1.5.3 Sun study: best supportive care (OS)

Methods

The Sun study[3] is summarised in CS section A.6.4. In summary, this was a retrospective chart review of patients who underwent surgical resection and postoperative radiotherapy for primary or recurrent CSCC of the head and neck between 1st January 1995 and 31st

December 2014 in the United States. The study included 72 patients, of whom 32 were immunocompetent and 40 were immunosuppressed. Among the immunocompetent patients, 20 had unresectable lesions that would be reflective of a BSC population relevant to the current appraisal. The remaining 52 patients (40 immunocompromised and 12 immunocompetent with resectable lesions) were excluded from analysis by the company which the ERG agree is appropriate. Baseline characteristics are only reported in the study publication for the 32 immunocompetent patients. The company assume that the baseline characteristics would be similar between immunocompetent patients irrespective of whether their lesions were resectable or unresectable; the ERG's clinical experts agreed this assumption is reasonable.

The Sun study excluded patients with distant metastatic disease at diagnosis, squamous cell carcinoma in situ alone, patients who had trunk or extremity tumours, and palliative doses of radiotherapy. As such, the study excludes some people who would be classified as receiving best supportive care, and thus provides a relatively narrow BSC population. We note that locoregional recurrence was defined in the Sun study as recurrence at the primary site, resection margin, or regional lymph nodes. Spread to regional lymph nodes would be classified as mCSCC according to the company's definitions of disease severity, so locoregional and distant as employed in the Sun study do not correspond to laCSCC and mCSCC as employed by the company. As noted in Appendix 3 below the ERG were unable to identify the source of laCSCC and mCSCC baseline characteristics reported in the CS for this study.

Company and ERG assessments of study validity

The CS does not provide an assessment of study validity. The Sun study has a similar design to the Jarkowski study, with similar limitations: small sample size (N=20), high risk of bias due to the retrospective selection of cases, and unclear generalisability due to having a non-UK population. Few baseline characteristics are reported in the Sun study that could be compared with the company trials (primarily age, gender, tumour location and T-stage) but these limited population characteristics are similar to those of the company trials (Appendix 3). As the key threats to validity are readily discernible the ERG did not consult published risk of bias tools to explore threats to validity in further detail.

Results

Aside from the median age (73 years) in the Sun study, which is comparable to that of the company cemiplimab trials (72 years), it is difficult to compare the baseline characteristics of

the studies because limited details were reported (Appendix 3). Results from the Sun study are only available for OS. The study paper reports that median survival of the 20 immunocompetent patients who had unresectable lesions was 5.0 months, whilst that of the 16 immunosuppressed patients with unresectable lesions was 3.9 months.[3] As would be expected, OS in the Sun study was lower than in the chemotherapy studies (Jarkowski study and the company chart review) (CS Table 68 and Table 4 above). However, results of these studies are uncertain due to the numerous limitations discussed above.

ERG conclusion

Despite having major limitations, the Sun study is the only source of BSC data for this appraisal (company base case).

3.1.6 Indirect treatment comparison methods

No studies directly comparing cemiplimab against chemotherapy or best supportive care are currently available. The company therefore employed indirect treatment comparison methods to compare the company cemiplimab trials against the three single-cohort comparator studies described above.

3.1.6.1 Identification of covariates for adjustment

Clarification responses A14 and A15 confirm that the targeted search for prognostic factors referred to in CS section A.7.1 is the same search that was reported in the previous appraisal TA592. The ERG identified a recent systematic review of prognostic factors for head and neck CSCC[13] and we also sought clinical expert opinion. We conclude that the company have identified the relevant prognostic factors as covariates for inclusion in their indirect treatment comparisons. However, as noted in the CS and Chart Review Report,[12] these variables were not consistently reported in the comparator studies, limiting the number of covariates that could be adjusted for in the analyses to a maximum of eight: median age; sex (% male); disease severity (% with laCSCC or mCSCC); tumour differentiation (% in each class); tumour location (% head/neck, trunk, or extremities); ECOG Performance Score (0, 1, 2); % who received prior systemic therapy; and tumour T-stage (% in each class) (Appendix 5).

For unanchored ITCs both prognostic factors and effect modifiers should be accounted for, [14] although the company considered that incorporating effect modifiers was not feasible due to the limited sample size and they acknowledge this as a limitation of the analyses (Chart Review Report section 5). We note that several of the included covariates are probable

effect modifiers (e.g. age, gender and performance status) and due to limitations of the available data it would not be feasible to include further covariates.

3.1.6.2 Summary of the indirect treatment comparison methods

The company employed four statistical approaches for adjusted indirect comparisons: inverse probability of treatment weighting (IPW), simulated treatment comparison (STC), matched-adjusted indirect comparison (MAIC), and multivariable regression (MVR) (described in more detail in sections 3.1.6.3 to 3.1.6.5 below). These are all forms of "unanchored" indirect comparison which can be used to estimate relative treatment effects by comparing single-arm studies. These statistical approaches aim, as far as is possible, to minimise bias in the measured outcomes (confounding) that results from imbalances in covariates between the studies under comparison.

The company also present naïve (unadjusted) comparisons of cemiplimab against chemotherapy and best supportive care alongside each of these analyses. Naïve comparisons are highly likely to produce biased outcomes, because imbalance in confounding covariates is not accounted for.[14] However, DSU Technical Support Document 18 recommends that results of naïve comparisons should be presented as supporting information alongside those of adjusted indirect comparisons.[14]

An overview of the ITC approaches employed by the company is provided in Table 6, showing which analyses inform the economic analysis. IPW and multivariable regression are appropriate where individual participant data (IPD) are available for both of the studies under comparison.[15] The STC and MAIC analyses are appropriate when IPD are available for one of the studies being compared and aggregate data are available for the comparator study.[14]

Table 6 Overview of the comparators and analysis approaches employed in the company's ITC analyses

Comparator study	Included in TA592?	Full IPD available? [a]	Analysis employed in the current CS	Outcomes analysed
Chemotherapy – company chart review [12]	No	Yes	Main analysis: IPW to estimate the average treatment effect in the treated (ATT). **This analysis informs the economic model** (CS Table 12). Scenario analysis: IPW to estimate the average treatment effect in the comparator (ATC). Scenario analysis: Multivariable regression (summarised in the Chart Review Report[12] but not discussed in the CS). Scenario analysis: Naïve comparison	Overall survival
Chemotherapy – Jarkowski study[11]	Yes	No	Main analysis: STC. [a] **This analysis informs the economic model** (CS Table 12). Scenario analysis: MAIC [a] Scenario analysis: Naïve comparison [a]	Overall survival Progression-free survival
Best supportive care – Sun study[3]	No	No	Main analysis: STC. **This analysis informs the economic model** (CS Table 12). Scenario analysis: MAIC Scenario analysis: Naïve comparison	Overall survival

IPD: individual participant data; IPW: inverse probability of treatment weighting; MAIC: matched-adjusted indirect comparison; STC: simulated treatment comparison

[a] This refers to participant-level data for the covariates, i.e. not including the limited IPD that were reconstructed by the company by digitising published KM curves in the Jarkowski and Sun studies to determine survival and censoring times (CS section A.15.9).

[b] This is the same as the approach employed in TA592.

The ERG agree with the company's overall strategy for indirect comparisons:

- The selection of the method (i.e. the choice of IPW, MVR, STC or MAIC) is broadly consistent with the approaches recommended in the DSU Technical Support Documents.[14 15]
- The company have attempted to include as many prognostic covariates as possible and have explored the statistical models that provide the best balance of covariates, acknowledging that analyses are limited by the availability of data on the covariates.

However, each of the ITC analyses has substantial limitations, which we discuss below for each analysis approach (sections 3.1.6.3 to 3.1.6.5).

The CS does not discuss the multivariable regression analysis when reporting results of the ITCs (CS Table 27). The best-fitting multivariable regression model (a marginal model based on backward selection of covariates) provided hazard ratios which according to their wide confidence intervals were not significantly different from 1.0 (Chart Review Report Table 5), although the company regard this as an exploratory analysis only due to model instability. The ERG believe that, due to limitations of the data, difficulty in selecting models, and the relatively wide range of hazard ratios produced by the models (Chart Review Report section 4.3) the MVR approach is less suitable than the IPW approach for indirect treatment comparisons in the present CDF review. We therefore do not discuss the MVR results further in this report.

3.1.6.3 Cemiplimab (company trials) versus chemotherapy (company chart review): IPW method

Summary of the statistical method

The company employed IPW based on propensity scores to improve the balance of covariates between the company trials for cemiplimab and the company chart review for chemotherapy) (CS section A.7.1). Propensity scores are defined as the predicted probability of treatment based on relevant covariates and were derived by the company using a logistic regression of treatment assignment (membership of the company trials or chart review) against a set of measured baseline covariates. These covariates were chosen because they were considered prognostically important (see section 3.1.6.1).

The IPW approach uses a patient's propensity score to generate a weight for each patient as summarised in section 3.2.1.2 of the company's Chart Review Report.[12] Using the IPW approach, patients from one study can be reweighted to match the baseline covariates of

those in the other study, thereby balancing the covariates between the studies to reduce the risk of baseline characteristics being confounded with the outcome (i.e. reduce the risk that effects on OS or PFS are explained by prognostic covariates rather than by cemiplimab or chemotherapy treatment). The reweighting approach was used by the company to estimate two different treatment effects:

- The **average treatment effect in the treated (ATT)**: Patients who received chemotherapy in the company chart review (i.e. the comparator population) were reweighted to match the baseline characteristics of those who received cemiplimab in the company trials (i.e. the treatment population). The ATT is an estimate of the treatment effect that would have been observed if the chart review patients had the same baseline characteristics as those enrolled in the company trials. This is the relevant analysis if the target population of interest is patients enrolled in the cemiplimab trials.
- The **average treatment effect in the comparator (ATC)**: Patients who received cemiplimab in the company trials (i.e. the treatment population) were reweighted to match the baseline characteristics of those who received chemotherapy in the company chart review (i.e. the comparator population). The ATC is an estimate of the treatment effect that would have been observed if the patients who were enrolled in the company trials had the same baseline characteristics as those in the company chart review. This is the relevant analysis if the target population of interest is patients in the real-world UK clinical practice (assuming that the company chart review population reflects that seen in UK clinical practice).

The company explored ATT and ATC models with varying inclusion of covariates (Appendix 5). The “full model” was designated the ATT or ATC model that incorporated the full set of available covariates. Ten further ATT and ATC models incorporating different combinations of the covariates were run, numbered sequentially 1-10 according to their statistical fit, with ATT model 1 having a better fit than ATT model 2 and so on (see ‘Assessment of model fit’ below). In the CS and Chart Review Report[12] the company focus mainly on the full ATT model and ATT model 1, and the full ATC model and ATC model 1 which the ERG agree is appropriate since these optimise both the incorporation of covariates and the statistical fit. To reduce the influence of extreme weights which lead to poor covariate balance, the company ran each analysis again, with trimmed weights capped at the 95th percentile (“trimmed analysis”), and explored whether this improved the model fit.

Assessment of model fit

The aim was to select the propensity score model with weights that resulted in the best balance of the key relevant covariates. The main parameters used for this judgement are the balance statistic (higher values indicating greater homogeneity of the covariates after reweighting); effective sample size (ESS; higher values are preferable); the proportion of covariates which had a low (<10%) or high (≥10%) absolute standardised difference (ASD) between the studies after reweighting (Appendix 6); and histograms of the distributions of patient weights (Chart Review Report Figures 2-3, C10-C18, D1-D2, D14-D22).

Appropriateness of the target population

The company preferred to use the ATT approach for their "base case" IPW analysis and the ATC approach in sensitivity analyses (CS section A.7.1). The ERG believe that the target population should be patients in a real-world clinical setting, so the ATC analysis would be logical as the base case analysis (provided that the company chart review population can be assumed to reflect that seen in UK clinical practice).

Appropriateness of the statistical models and assumptions

- The ATT and ATC analyses are standard statistical analysis approaches derived from causality theory and the company's overall approach to the IPW analyses is consistent with TSD 17 guidance.[15]
- Calculation of hazard ratios requires that the assumption of proportional hazards (PH) is satisfied. The company present tests of the PH assumption in Chart Review Report Appendix E. Both the company (clarification responses A22-A25) and ERG agree that these tests suggest the PH assumption is violated for most if not all ITC comparisons (some subjectivity of interpretation is inevitable). The hazard ratios presented in the CS and ERG report are therefore uncertain and should not be used to infer relative treatment effects.
- The company did not model time-varying hazard ratios, for three reasons stated in clarification response A22 which the ERG agree are reasonable.
- Instead of using hazard ratios to provide relative treatment effects for the economic model, the model is informed by the separate IPW-adjusted KM curves which do not assume proportional hazards (clarification response A24). This is consistent with the approach employed in TA592.

Uncertainties in the ITC methods

Results of the IPW analyses comparing cemiplimab to chemotherapy are uncertain because:

- The company chart review population had a retrospective design with, post-hoc data selection, and has poor face-validity (section 3.1.5.1).
- IPW adjustment was not fully successful at balancing all the covariates (all analysis models had at least two covariates with a standardised absolute difference > 10% after reweighting: see Appendix 6).
- A maximum of eight prognostic factors could be included as covariates due to limited details being reported in the studies; prior radiation therapy was not included as a covariate in any analysis models (Appendix 5).
- HRs should be interpreted with caution due to lack of support for the proportional hazards assumption.
- The ERG do not have access to IPD for the company trials and company chart review and therefore cannot verify that the analyses were conducted as stated.

3.1.6.4 Cemiplimab versus chemotherapy (Jarkowski study): STC & MAIC

Summary of the statistical method

The company confirmed (clarification response A19) that the statistical methods applied for STC and MAIC to compare the company trials to the Jarkowski study were identical to those employed in TA592. The ERG agree that the company's rationale for selecting STC as the main analysis, with the MAIC and naïve analyses as scenarios is appropriate (TA592 ERG Report section 3.1.7.4). The company explored two models: a core model which incorporated two covariates (disease stage and tumour location) and an extended model which incorporated four covariates (disease stage, tumour location, gender and prior systemic therapy) (Tables 5 & 6 in clarification response A18). The company selected the core model as it had the better fit, but this was based on only a marginally lower Akaike Information Criterion (AIC) value for the STC analysis ([redacted] versus [redacted]) (Clarification response A18). The company report the OS and PFS curves produced by the STC and MAIC analyses (CS Figures 9 and 10) and corresponding hazard ratios (CS section A.7.2) but these are only for the core model. Given the closeness of the AIC values, and the larger number of covariates included in the extended model, the ERG suggest that STC and MAIC results for the extended model should also be provided.

Appropriateness of the target population

STC analysis simulates adding a "missing" trial arm such that outcome predictions are made for the company trial population using the mean characteristics of the Jarkowski study population. In the MAIC analysis the Jarkowski study is modelled as the target population

(i.e. company trial IPD are reweighted to match those of the Jarkowski study). Appropriateness of the target population is therefore contingent on the Jarkowski study population being reflective of that seen UK clinical practice which (as noted in TA592) is questionable given that the study was conducted in the USA. (NB it is difficult to compare the Jarkowski study with the UK SACT dataset to clarify its UK relevance due to the limited SACT population characteristics reported; Appendix 3).

Uncertainties in the ITC methods

Results of the STC and MAIC analyses comparing cemiplimab to chemotherapy using the Jarkowski study are uncertain because:

- The Jarkowski study has several limitations including retrospective design, small sample size and being a non-UK study (section 3.1.5.2).
- Only two covariates could be included in the core STC and MAIC model due to limited details being reported in the studies. Results of the extended model, which included four covariates, are not provided despite a similar model fit.
- As noted in the IPW analyses (section 3.1.6.3) the proportional hazards assumption is not supported for comparisons of cemiplimab against platinum-based chemotherapy and therefore hazard ratios would be unreliable for estimating relative treatment effects.
- The ERG do not have access to IPD for the company trials and therefore cannot verify that the analyses were conducted as stated.

3.1.6.5 Cemiplimab versus best supportive care (Sun study): STC & MAIC

Summary of the statistical method

The comparison of the company trials against the Sun study followed the same approach using STC and MAIC as for the comparison against the Jarkowski study described above (section 3.1.6.4). A core model incorporated four covariates (age, disease stage, tumour location and tumour stage) and an extended model incorporated a further three covariates (gender, ECOG performance score and prior radiation therapy) (Table 7 in clarification response A18). The CS does not discuss whether any intermediate models incorporating other combinations of covariates could have been developed. The AIC values favoured the extended model over the core model ([redacted] and [redacted] respectively) (clarification response A18). The company report the OS curve produced by the STC and MAIC analyses (CS Figure 11) and corresponding hazard ratios (CS section A.7.3) for the extended model

only. The ERG believe this is acceptable given that the core model included only four covariates, without improved model fit.

Appropriateness of the target population

As discussed above in section 3.1.6.4, appropriateness of the target population is contingent on the comparator study population, i.e. in this case the Sun study, being reflective of that seen in UK clinical practice. This is questionable given that the study was conducted in the USA. (NB it is difficult to compare the Sun study with the UK SACT dataset to clarify its UK relevance due to the limited SACT population characteristics reported; Appendix 3).

Uncertainties in the ITC methods

Results of the STC and MAIC analyses comparing cemiplimab to BSC are uncertain because:

- The Sun study population has several limitations including retrospective design, small sample size and being a non-UK study (section 3.1.5.3).
- As noted in Appendix 3 the ERG were unable to identify the source of disease severity (laCSCC and mCSCC) baseline characteristics provided by the company for this study.
- The proportional hazards assumption does not appear to be supported for the comparison of cemiplimab against BSC (CS Figure 25), although the company do not discuss this explicitly. Hazard ratios for this comparison therefore may be unreliable.
- The ERG do not have access to IPD for the company trials and therefore cannot verify that the analyses were conducted as stated.

3.1.7 Indirect treatment comparison results

As discussed above (sections 3.1.6.3 to 3.1.6.5) the proportional hazards assumption is not satisfied for most if not all ITC analyses, meaning that hazard ratios describing the relative treatment effects from the ITCs will be unreliable and should be interpreted with caution. The primary output from the ITCs which inform the economic model are the ITC-adjusted/weighted KM curves for OS and PFS which do not assume proportional hazards.

Cemiplimab versus chemotherapy: IPW and naïve analyses (OS)

The company report a range of KM curves, hazard ratios and model fit parameters for the eleven ATT models and the eleven ATC models, for trimmed and untrimmed analyses as summarised in Appendix 6. The main models likely to be of interest for the economic analysis are the full ATT model (Chart Review Report Figure 4), ATT model 1 (Chart Review

Report Figure 5), full ATC model (Chart Review Report Figure D3) and ATC model 1 (Chart Review Report Figure D4) since these optimise model fit and inclusion of covariates. The KM curves for all models indicate OS is higher with cemiplimab than with platinum-based chemotherapy; the models primarily differ in the degree of overlap of the confidence intervals for the curves.

For their base case economic analyses the company preferred ATT model 1 (see Table 7). This model included 5 covariates and appears to have a slightly better fit than the full ATT model which included 7 covariates (ATT model 1 has higher ESS and fewer reweighted covariates with ASD >10%, but a lower balance statistic – illustrating that decisions on model fit can be somewhat subjective) (Appendix 6). CS Figure 8 shows the weighted KM curve for chemotherapy (company chart review) compared against the KM curve for cemiplimab for ATT model 1. Both the trimmed and untrimmed analyses demonstrate that patients receiving chemotherapy in the company chart review had lower OS than those receiving cemiplimab in the company trials, as expected.

If the company chart review reflects a real-world UK clinical practice cohort it may be more appropriate to treat this as the target population of interest, i.e. using the ATC analysis approach. As shown in Appendix 6, it is difficult to separate the full ATC model and ATC model 1 based on the balance statistic, ESS, number of unbalanced covariates remaining after reweighting (trimmed analysis) or on the distribution of weights (Chart Review Figures D1 and D2) which were broadly similar for both models. The full ATC model has the advantage that it incorporates eight covariates whereas ATC model 1 incorporates seven. We note that the full ATC model incorporates one more covariate than the company's preferred ATT model 1 model and the histograms of weights are suggestive of a marginally better balance for the full ATC model than ATT model 1 (compare Chart Review Figures 1-2 versus D1-D2). However, it is important to stress that all ATT and ATC models had at least 2 covariates with absolute standardised exceeding 10% in trimmed analyses, indicating that none of the models was fully successful at balancing the covariates, meaning that for all models there is a residual risk of confounding.

The figures in the Chart Review Report which present the results of the ATT and ATC analyses also include naïve comparisons (i.e. unadjusted curves are included within the figures). Comparisons of the unadjusted cemiplimab and chemotherapy curves provide a similar interpretation to those of the adjusted curves, in all cases clearly showing OS to be higher with cemiplimab than with platinum-based chemotherapy. Results of naïve

comparisons are also presented as hazard ratios alongside those of the ATT and ATC model results in Chart Review Report Table 5. There is general overlap of the hazard ratios across the models, and the hazard ratios tend to be slightly higher for the trimmed analyses (Appendix 6) but these results should be interpreted with caution as the proportional hazards assumption is not supported.

ERG conclusion

Results of the IPW-adjusted ITC analyses are highly uncertain because the comparator study lacks face-validity (section 3.1.5.1) and none of the IPW models were fully successful at balancing all covariates (section 3.1.6.3). Hazard ratios do not assist interpretation since the proportional hazards assumption is not supported. It is unclear conceptually whether an ATT or ATC model would be most appropriate, since the extent to which the company chart review is reflective of UK clinical practice (external validity) is uncertain (the chart review aimed to collect data relevant to clinical practice, but the eligibility criteria for the chart review also aimed to match the population characteristics of the company trials). A critical consideration to enable causal inference is that the ITC outcomes should be free from confounding (high internal validity) and therefore IPW models should be selected which successfully balance the covariates. Given that none of the ATT and ATC models achieved this (Appendix 6) it is inadvisable to apply causal inference to these ITC results.

Cemiplimab versus chemotherapy: STC, MAIC and naïve analyses (OS and PFS)

The company preferred the core STC model to inform their economic analysis, but this incorporates only two covariates (disease stage [laCSCC or mCSCC] and tumour location [head and neck versus other]) (Clarification response Table 5). Results are only reported for the core model.

CS Figure 9 (OS) and CS Figure 10 (PFS) show the predicted cemiplimab KM curves from the STC and MAIC analyses for the core model, compared to the chemotherapy curve from the Jarkowski study. Both OS and PFS are higher for cemiplimab than for platinum-based chemotherapy, although for PFS the tails of the cemiplimab and chemotherapy curves overlap after 36 months where numbers at risk are small. Confidence intervals are missing from the KM curves so there is no indication of the uncertainty.

As noted above (section 3.1.6.4), the ERG believe OS and PFS results of the extended model which incorporates four covariates should also be presented for the comparison, given the similar model fit

The figures which present the results of the MAIC and STC analyses (CS Figure 9 for OS and CS Figure 10 for PFS) also include naïve comparisons (i.e. unadjusted curves are included within the figures). Comparisons of the unadjusted cemiplimab and chemotherapy curves provide a similar interpretation to those of the adjusted curves, in all cases clearly showing OS to be higher with cemiplimab than with chemotherapy. Hazard ratios from a naïve (unadjusted) comparison of the company trials against the Jarkowski study are compared against those from the STC and MAIC in CS section A.7.2. There is general overlap of the hazard ratios although these results should be interpreted with caution as the proportional hazards assumption is not supported.

ERG conclusion

Results of this ITC analysis are highly uncertain because of limitations in the comparator study (section 3.1.5.2), use of a suboptimal model that incorporates only two covariates (section 3.1.6.4) and absence of confidence intervals for the KM curves so the uncertainty is not displayed. The ERG suggest that the extended model results should have been provided alongside those of the core model, with confidence intervals provided for all KM curves.

Cemiplimab versus BSC: STC, MAIC and naïve analyses (OS)

The company preferred the extended model for STC to inform their economic analysis. The extended model incorporates 7 covariates and appears to have a better fit (lower AIC) than the core model (which incorporates 4 covariates) (clarification response Table 7).

CS Figure 11 shows the predicted cemiplimab KM curves from the STC and MAIC analyses for the extended model, compared to the best supportive care curve from the Sun study. There is some disagreement between the STC and MAIC curves, with the STC more closely matching the observed cemiplimab data. Both curves clearly demonstrate higher OS with cemiplimab than with best supportive care. However, the company note that the extended model resulted in a substantially reduced ESS of [redacted], indicating an overall poor model fit (clarification response A21).

A visual naïve comparison of the unadjusted KM curves for cemiplimab and chemotherapy is provided in CS Figure 11, which is consistent with the results of the STC and MAIC analyses. Hazard ratios from a naïve (unadjusted) comparison of the company trials against the Sun study are compared against those from the STC and MAIC in CS section A.7.3. There is general overlap of the hazard ratios but these results should be interpreted with

caution as it appears unlikely that the proportional hazards assumption is supported for comparison of cemiplimab against BSC.

ERG conclusion

Results of this ITC analysis are highly uncertain because of limitations in the comparator study (section 3.1.5.3), poor model fit, and absence of confidence intervals for the KM curves so the uncertainty is not displayed. The ERG suggest that confidence intervals should be provided for all KM curves.

3.2 Safety

The Terms of Engagement do not specify safety monitoring. The ERG requested an update on adverse events given that longer follow-up is now available in the company trials. A summary of adverse events up to an October 2020 data cut are provided in Table 9 of the clarification response document since formal statistical analysis of safety data has not been performed for the July 2021 data cut (clarification response A28). The October 2020 data do not identify any new safety concerns and demonstrate comparable safety between the weight-based and flat dose groups within the EMPOWER CSCC-1 study (as stated in clarification response A27). The company confirmed that safety data were not collected in the SACT dataset (clarification response A29).

3.3 Additional work on clinical effectiveness undertaken by the ERG

The company provided details of their updated systematic literature review on 4th February 2022 (clarification response A1). Meanwhile, the ERG carried out brief searches to identify whether any new evidence published since the original appraisal was missed. See section 3.1.1 of this report for details.

3.4 Conclusions of the clinical effectiveness section

New evidence

- The company have identified all relevant studies. New evidence is available from 4 sources: an updated data cut in the company trials (cemiplimab), SACT dataset (cemiplimab), company chart review (chemotherapy), and Sun study (best supportive care). Existing data from a previous study included in the TA592 appraisal (Jarkowski, chemotherapy) were also used in a scenario analysis.

SACT dataset

- The ERG's clinical experts confirmed that the SACT dataset is reflective of current clinical practice and is therefore suitable as a benchmark against which to assess the external validity of the company clinical trials. However, patient behaviour and clinical practice represented in the SACT dataset are likely to reflect the impact of the covid-19 pandemic.
- There are differences between the company trials and SACT dataset. The SACT dataset reflects that an older, frailer population with comorbidities such as autoimmunity can be treated with cemiplimab in practice. Overall survival in the SACT dataset is lower than in the company trials, likely reflecting the younger, fitter population enrolled in the company trials.

Comparator studies

- The three comparator studies (company chart review, Jarkowski study, Sun study) all have major limitations. The company chart review contains data and assumptions which the ERG's three clinical experts considered clinically implausible, as well as missing data, and the company themselves regard the chart review as having "poor face-validity". The company, ERG and ERG's clinical experts concur that the population characteristics and results of the chart review are highly uncertain.
- The Jarkowski and Sun studies are both small (N≤20), retrospective, and conducted in the USA therefore of questionable reliability and relevance to UK clinical practice. The population characteristics and results of these studies are therefore also highly uncertain.
- These limitations mean that none of the included studies provide a reliable estimate of the effects of chemotherapy or of BSC in a UK setting. Thus, uncertainties in these comparators have not been reduced relative to the pre-CDF appraisal TA592.

Indirect treatment comparisons

- The company used indirect treatment comparisons to compare the company trials (cemiplimab) against the comparator studies, i.e. the company chart review (chemotherapy, OS), the Jarkowski study (chemotherapy, OS and PFS), and the Sun study (best supportive care, OS). Three methods of indirect treatment comparison were employed (IPW approach, STC and MAIC) which are appropriate for the types of data available.

- The ITC analyses are all limited by the high uncertainty in the population characteristics and results of the comparator studies that they included, rendering the results of the ITC analyses themselves highly uncertain.
- Additionally, the ITC methods are subject to uncertainty, primarily due to the inability of ITC models to balance all measured prognostic covariates (IPW approach), and lack of sufficient data to enable sufficient prognostic covariates to be modelled (STC and MAIC approaches).
- The IPW approach estimated the average treatment effect in the treated (ATT) and the average treatment effect in the comparator (ATC) which provides an opportunity to select which study represents the target population of interest (i.e. the company trials according to the ATT approach, or the chart review according to the ATC approach). Unfortunately, the poor face validity of the chart review study makes it unclear whether the chart review reflects a UK clinical practice population and hence whether an ATC model would be more appropriate than the company's preferred approach which uses an ATT model. In practice, however, all models failed to adequately balance the prognostic covariates so their results are at high risk of confounding.
- Hazard ratios obtained from the ITCs require the proportional hazards assumption to be satisfied. This assumption does not hold for the ITCs comparing cemiplimab against chemotherapy and appears unlikely to hold for the comparison of cemiplimab against BSC. Hazard ratios therefore cannot be relied upon to assist interpretation of the ITC results, which is primarily limited to the visual inspection of KM curves.

Summary

Whilst the company have largely adhered to the Terms of Engagement, the new evidence from comparator studies provided for this CDF review has not reduced the uncertainty in the effectiveness of cemiplimab as used in the UK compared to platinum-based chemotherapy and BSC. The longer-term data available from the EMPOWER-CSCC 1 trial have limited value in establishing relative effectiveness of cemiplimab since comparable long-term data do not exist for the comparator studies.

The areas where uncertainty has been reduced are:

- Improved confidence in the stopping rule and improved follow up of survival outcomes in the trial setting as a result of longer-term data being available in the EMPOWER-CSCC 1 trial.

- The SACT dataset has also helped to establish that the company cemiplimab trials lack generalisability to UK clinical practice. However, the SACT dataset has limitations due to relatively few population characteristics collected, whilst the overlap between the SACT dataset and COVID-19 pandemic could influence generalisability of the SACT data.

4 COST EFFECTIVENESS

4.1 Model structure

In response to clarification question B1, the company submitted a revised version of their CDF review model capable of replicating the ICERs used in the committee's decision making at the point of CDF entry. All discussion and results reported below relates to this revised CDF review model (version 8 submitted 8 February 2022).

The model has a partitioned survival structure with 3 health states: pre-progression, post-progression and death, which the TA592 committee considered acceptable. This structure has not changed for the CDF review. The company have made some minor corrections and changes to model assumptions and parameters, listed in Table 7 below. We critique these changes the in the following sections of this report.

Table 7 List of changes to the company model for the CDF review

Change to model	Location in submission	ERG discussion
Population baseline characteristics		
Mean age (71.2 years) and gender (83.1% male) from 2021 trial data cut (includes flat dose group)	CS Table 35	4.2 below
Overall survival extrapolations		
Cemiplimab: company trial data updated to July 21 (no change to log-normal survival function)	CS A.8.3.1 and Table 15	4.5.2 below
Chemotherapy: UK Chart Review [12], ATT model 1 trimmed, log-logistic survival function	CS A.8.3.2, Table 15 and Clarification Response B2	
BSC: Sun et al. 2019 [3], STC analysis with log-logistic survival function	CS A.8.3.3 and Table 15	
General population mortality cap: updated to 2018-2020 life tables, with gender-specific population	CS A.15.13 and model	
Progression free survival extrapolations		
Cemiplimab: company trial data updated to July 2021, fractional polynomial (p1 = 0 p2 = -1) survival function	CS A.8.4.1 and Table 15	4.5.3 below
Chemotherapy: no change to data source (Jarkowski et al. 2016)[11] or survival function (Weibull).	CS A.8.4.2 and Table 15	
BSC: patients start in post-progression state	CS A.8.4.3 and Table 15	
Waning of treatment effect on OS and PFS		
Duration of cemiplimab relative effects extended to 60 months. (No change to 2-year stopping rule).	CS A.8.5	4.5.4 below
Adverse event rates		

Cemiplimab rates updated to July 2021 trial data.	CS Table 34	4.5.4 below
Exclusion of adverse events with <5% incidence	CS A.15.13	
Utilities		
Updated EORTC QLQ-C30 from company trials with October 2020 data cut (no change to mapping)[16]	CS Table 33	4.7 below
Correction to cap for age-related utility decrement for PFS health state, and inclusion of multiplicative option.	CS A.15.13	
Resource use and costs		
Cemiplimab PAS price discount [redacted] per 350 mg vial).	CS Table 2	4.8 below
Unit costs updated: 2021 eMIT, 2019/20 NHS Reference Costs, 2020 PSSRU and inflation (NHSCII index)[17-19]	CS A.15.12	

4.2 Population

The modelled cohort is based on the population in the cemiplimab trials. The company revised the baseline patient characteristics in their base case to reflect the dataset in the CDF review, which includes an additional patient group allocated to a flat dose of cemiplimab in EMPOWER (CS section A.6.1.1). This increased the mean age of the modelled cohort from 70.44 years in TA592 to 71.16 years in the CDF review (CS Table 35), which causes a small increase in the ICERs.

The model uses separate sources for survival outcomes with cemiplimab (company trials), chemotherapy (chart review and Jarkowski study) and BSC (Sun study), which is a potential source of bias. The company attempt to adjust for population differences in their ITC analyses but results of the ITCs are highly uncertain due to limitations of the comparator studies and residual imbalances in prognostic factors (see discussion in sections 3.1.6 and 3.1.7 above).

The committee noted that the modelled cohort in TA592 (based on the cemiplimab trials) did not completely represent patients expected to have cemiplimab in UK clinical practice. The company state that baseline characteristics in the CDF review model are thought to be generalisable to the UK patient population "*as demonstrated in the SACT dataset and the chart review study*" (CS section A.14.3). But they go on to note differences between the trial and real world populations: the latter being generally older and frailer, with more prior systemic therapy and autoimmune comorbidities.

For the base case comparison with chemotherapy, the company use an ATT model: adjusting survival with chemotherapy from the chart review to reflect the population in the cemiplimab trials. They also present a scenario with an ATC model: adjusting the cemiplimab trial data to reflect the population in the chart review (CS Table 20). This raises the question of which approach best reflects outcomes in UK practice (see section 3.1.7.1).

There are particularly notable differences between the patients in the cemiplimab trials and those treated with cemiplimab in the SACT dataset (CS Table 23).[4] The company report a scenario with SACT demographics (median age 77 years and 74% male), which increases the ICERs for cemiplimab (CS Table 20). The company have not included SACT survival data in the model, arguing that the trial provides 'more robust longer term trial data' (CS Table 9).

Results from the SACT dataset so far indicate that survival has been worse under the CDF (median OS 21 months) than in the trial [redacted] alive at [redacted] months). The company present various explanations for these differences in survival, including the patient populations and the impact of COVID-19 on clinical presentation and treatment (CS section A.6.5).

ERG conclusions

- The SACT dataset comprises patients treated with cemiplimab in UK practice. This indicates that clinicians will offer cemiplimab to patients who are on average older and less fit than those in the trials, and also that patients with some degree of immunocompromise may be offered cemiplimab. This view is supported by expert advice to the ERG. We therefore prefer the company's scenario with baseline patient characteristics derived from the SACT dataset (median 77 years of age, 74% male).
- There is uncertainty over the comparability of the populations in the cemiplimab trials and the chart review, and which source is more generalisable to UK practice. The 'real world' chart review should better reflect UK practice, but it is subject to bias due to problems of face-validity including missing and ambiguous data and post hoc exclusion of patients from the analysis. This uncertainty translates to uncertainty over which IPW method (ATT or ATC) should be used to adjust for prognostic factors. Although there is a more fundamental uncertainty, as the ERG does not have confidence that any of the ATT or ATC models successfully balanced all covariates (see Section 3.4 above.

4.3 Interventions and comparators

4.3.1 Cemiplimab

The base case uses survival curves for cemiplimab estimated from the company's trials, including groups 1 and 2 treated with a weight-based dose and group 3 treated with a flat dose in the EMPOWER-CSCC 1 trial (CS Table 5). In response to clarification question A2, the company provided a provisional comparison of outcomes between the three groups, see section 3.1.2 above. The model uses costs for cemiplimab based on the flat dose of 350 mg IV every week recommended in the marketing authorisation.

The model assumes that all patients continue treatment until progression or a maximum of 24 months, as recommended in TA592. The analysis does not account for patients who may stop treatment before progression, for example because of adverse effects. The maximum duration of treatment in the company's trials was 22 months (shorter for the fixed dose group). The CDF submission does not report the duration of treatment in the cemiplimab trials, but median PFS was [redacted] (CS section A.6.1.3).

4.3.2 Platinum-based chemotherapy

The NICE committee concluded that platinum based chemotherapy and best supportive care are both relevant comparators for cemiplimab (TA592 section 3).

The company agree, but state that UK clinical opinion is that BSC may be considered a more relevant comparator, as cemiplimab can be used for patients who cannot tolerate chemotherapy (CS section A.1). This view is supported in the submission by the British Association of Dermatologists, who state that in the UK very few patients will be offered EGFR inhibitors or chemotherapy (BAD submission p5).

A clinical expert advising the ERG reported that although patients were occasionally treated with platinum based chemotherapy prior to the availability of cemiplimab, many more patients are suitable for treatment with cemiplimab. Another expert noted that the views of dermatologists and/or oncologists in different centres in the UK may differ regarding which patients would be suitable for chemotherapy or which individual patients in the dermatology clinic should be offered the option of chemotherapy.

4.3.3 Best supportive care

The company excluded patients on BSC from the Chart review analysis and instead relied on data for the 20 immunocompetent patients in the Sun study for their base case analysis. They also report a scenario with survival outcomes for BSC based on data for chemotherapy from the Jarkowski study (as in the analysis for TA592).

ERG conclusions

- The company do not report a full incremental analysis between cemiplimab, chemotherapy and BSC. The ERG consider that this is reasonable because, although clinical advice suggests that cemiplimab is likely to provide an alternative for patients who would otherwise have chemotherapy and for those who would have BSC, these groups of patients may be considered as largely distinct.
- The model reflects the TA592 recommendation for a maximum 24-month stopping rule for cemiplimab, but with the assumption that no patients stop treatment prior to disease progression. This latter assumption does not reflect experience from the SACT dataset and is likely to overestimate the costs of cemiplimab.
- There is very sparse data on outcomes with BSC, as patients treated with BSC were excluded from the UK chart review and the Sun study cohort is limited. There is therefore high uncertainty over the cost-effectiveness estimates for the comparison with BSC.

4.4 Perspective, time horizon and discounting

The model uses a lifetime horizon (30 years from an initial mean age of 71 years in the base case). In accordance with the original submission and the NICE reference case, costs are estimated from the perspective of the NHS and personal social services and a discount rate of 3.5% per year is applied to both costs and QALYs. The model uses a monthly cycle, with a half-cycle correction.

4.5 Treatment effectiveness and extrapolation

4.5.1 Overview of methods for survival extrapolations

The company outline their approach to estimating PFS and OS in CS section A.8.2. As in the original submission, they fit independent survival curves from separate single-arm data sources for cemiplimab, chemotherapy and BSC.

Evidence regarding the proportional hazards assumption for OS and PFS comparisons is

presented in CS A.15.2 and A.15.3, including log-log plots and hazard plots. Additional information, including Schoenfeld residual plots, is provided in the technical report on the UK chart review (Sanofi 2021).[12] See discussion in sections 3.1.6.3 and 3.1.7 above.

The comparisons are adjusted for population differences, using methods described in CS section A.7 and Appendices A.15.8 and A.15.9, see discussion in section 3.1.6 above. The economic model uses the IPW and STC approaches:

- For the comparison with chemotherapy, OS is estimated from IPD from the company trials and the chart review, with IPW-based indirect comparisons used to weight the data to achieve similar population characteristics for the two data sources (CS sections A.7.1 and A.15.8), as explained in section 3.1.6.3 above. The base case uses an ATT approach (chart review results adjusted to reflect the trial population), with ATT model 1 as the preferred model (CS Table 10). The company also report scenarios with the full ATT model and ATC model 1 (CS Table 20). All economic analyses use 'trimmed' weights, capped at the 95% percentile.
- The Jarkowski study cohort provides another data source for chemotherapy. This is used in the base case for PFS, which is not available from the chart review, and as a scenario for OS. The company only include the STC method of population adjustment in the economic model. For this analysis, results for cemiplimab are adjusted to reflect characteristics of the Jarkowski cohort (analogous to an ATC approach). As noted in section 3.1.5.2 above, the ERG has concerns over the robustness of this analysis due to limitations in the face validity of the comparators and lack of covariates to adequately match the populations.
- For the comparison with BSC, OS is estimated from the Sun study cohort, using the STC method to adjust the cemiplimab results to reflect characteristics of the Sun cohort (CS section A.7.3). This source does not report PFS and the company make an assumption that the BSC population start in a progressed health state (CS A.8.4.3).

Finally, the company fitted survival distributions to the (population adjusted) data (CS section A.8.2). For each survival outcome, four parametric distributions (Weibull, Gompertz, log-normal and log-logistic) and ten fractional polynomial (FP) distributions were fitted. The company reported following the steps recommended in NICE DSU guidance (TSD 14 and 21) to select preferred distributions for OS and PFS: assessment of statistical (AIC/BIC) and visual fit to KM data; assessment of the shape of the hazard over time, and consideration of the plausibility of the extrapolations (clinical expert opinion from an advisory board).

However, they did not explore uncertainty over the choice of survival distributions in scenario analysis.

4.5.2 Overall survival extrapolations

Cemiplimab OS (CS section A.8.3.1)

- Fitted to unadjusted integrated trial data (CS Figure 1).
- Log-normal distribution (as in TA592): best AIC/BIC statistics (CS Table 24), good visual fit (CS Figure 32) and decreasing hazards (CS Figure 45).

Platinum based chemotherapy OS (CS section A.8.3.2)

- Chart review data, adjusted for trial population (IPW ATT model 1, trimmed analysis).
- Log-logistic distribution: revised from Gompertz fitted to Jarkowski data in TA592.
- Note that there is a reporting error in CS section A.8.3.2 and CS Table 15, as confirmed in the company's response to clarification question B2. However, without a correction to the text it is difficult to understand the rationale for the company's choice of log-logistic distribution for their base case. The model fit statistics for the base case model are also missing from CS Table 24 and it is very difficult to assess the visual fit to the KM data (CS Figure 37) or the trends in hazards (CS Figure 50), given the scale and numbers of series shown on these graphs.
- From visual inspection in the model, it does appear difficult to reconcile fit to the chart review KM curve with the 3-5 year life expectancy estimated by the company's advisory board. The distributions with a better fit to the chart review data have a plateau in long-term survival.

Best supportive care OS (CS A.8.3.3)

- Fitted to the Sun study data for immunocompetent patients (n=20), with STC adjustment of the cemiplimab curve to reflect Sun study population characteristics.
- Log-logistic distribution chosen, based on clinical opinion (survival landmarks for BSC). This is not the best-fitting distribution.
- In TA592, the same OS curve was used for BSC as for chemotherapy (Jarkowski study, Gompertz distribution due to the lack of other data.

General population mortality rates

- Updated for 2018-2020 National Life Tables, England and Wales (ONS).[20]

- Applied as a lower limit to the modelled mortality rates, as in the TA592 model.

4.5.3 Progression free survival extrapolations

Cemiplimab PFS (CS section A.8.4.1)

- Fitted to updated integrated trial data (CS section A.6.1.3; CS Figure 2)
- Second order fractional polynomial (p1 = 0, p2 = -1) chosen based on the statistical fit and advice on clinical plausibility of the extrapolations from the company's clinical advisory group.
- The company note that the Weibull distribution used in TA592 had the poorest statistical fit to the updated cemiplimab trial data.

Platinum based chemotherapy (CS section A.8.4.2)

- Base case: Jarkowski STC analysis (CS section A.6.3; CS Figure 5), Weibull distribution (as in TA592)
- PFS data from the chart review were not considered reliable (44/47 PFS events were deaths).
- Company argues similarity of chart review and Jarkowski populations (CS section A.6.2.1) and OS results (CS section A.6.2.2; CS Figure 4).

Best supportive care (CS section A.8.4.3)

- BSC is assumed to be palliative; all patients start in a post-progression state.

4.5.4 Waning of treatment effects

The company describe their approach to modelling the waning of treatment effects in CS section A.8.5. The analysis at CDF entry (TA592) had assumed waning of the relative treatment effects of cemiplimab (equal hazards for progression and mortality) at 36 months.

The revised CDF review company base case assumes loss of relative benefit at 60 months, based on the maximum follow up of EMPOWER-CSCC 1 trial data for cemiplimab. The CS presents two scenarios to test less conservative assumptions:

- No waning, with continuation of fitted OS and PFS extrapolations for cemiplimab.
- Gradual waning between 60 to 96 months.

ERG conclusions

- A high degree of uncertainty remains over the survival extrapolations in the CDF review model due to limitations in data for the comparators, and reliance on data from different populations and healthcare contexts.
- The company fit independent survival curves to separate data sources for each comparator in the economic model, rather than using relative treatment effects (hazard ratios) estimated from the population adjusted indirect comparisons. This is reasonable, as proportional hazards are not supported, but the ERG has serious concerns over whether the any of the methods of population adjustment for the indirect comparisons (IPW and STC) provide an adequate balance of prognostic covariates (see section 3.4 above).
- The base case OS extrapolation for chemotherapy is adjusted to align with the population in the cemiplimab trials (ATT analysis), which does not reflect the population treated with cemiplimab in practice under the CDF (SACT dataset). However, the generalisability of the alternative ATC scenario is also questionable.
- The reported methods for fitting survival extrapolations are consistent with guidance.[21 22] However, the rationale for the company's choice of the log-logistic distribution for chemotherapy OS is not clearly explained and they do not explore the impact of using alternative survival distributions. We consider a range of alternatives in ERG scenario analysis, see section 6.1 below.
- Company assumptions used to estimate PFS for the comparators are also uncertain. For chemotherapy, they use different sources for OS (chart review) and PFS (Jarkowski study). And for BSC they assume that all patients start in the post-progression state. We explore another approach in an ERG scenario analysis, using the relationship between PFS and OS in the Jarkowski study (see section 6.1 below).
- The company's approach to modelling waning of the relative treatment benefit for cemiplimab is consistent with that in TA592. They have assumed a longer persistence of the advantage in their updated base case (5 rather than 3 years), based on extended data from EMPOWER. Alongside company scenarios with no waning and gradual waning between 5 and 8 years, we report additional ERG scenarios to test the impact of earlier loss of relative effects (see section 6.1 below).

4.6 Adverse effects

The company have updated adverse event rates for cemiplimab from the July 2021 EMPOWER-CSCC 1 trial data cut (CS A.15.9 Table 34). Incidence of 'failure to thrive' and fatigue were set to zero, as the observed rates did not reach the 5% threshold for inclusion

(CS A.15.13). The change in adverse event rates has a minimal impact on the cost-effectiveness results.

4.7 Health related quality of life

Utility estimates were also updated, based on EORTC quality of life data from the EMPOWER-CSCC 1 trial October 2020 data cut (CS section A.15.10). As in the TA592 analysis, data were mapped to EQ-5D-3L UK tariff values using the algorithm reported by Longworth et al. (2014).[16] [redacted] (CS Table 33).

The model includes a cap on utility that prevents utilities exceeding general population values (adjusted for age and the gender split). The company made a correction to the way in which this utility cap was applied. The ERG agree with this correction.

4.8 Resources and costs

The model includes a revised price discount for cemiplimab ([redacted] at CDF entry to [redacted] in the present analysis). A list of resource use and unit cost parameters is provided in CS Table 35. Resource use assumptions have not been changed from those in the analysis at CDF entry. Unit costs have been updated for all drugs in the model, drug administration, monitoring, adverse events and other resource use.[17-19]

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Deterministic base case

The company's deterministic base case results are reported in CS Section A.10, Tables 16 and 17. Revised versions of these tables provided in response to ERG Clarification Question B1 show the correct ICERs for cemiplimab at CDF entry, as specified in the terms of engagement for the CDF review: £45,693 per QALY compared with chemotherapy; and £47,463 per QALY compared with BSC (see Table 8).

Table 8 Cost effectiveness results at CDF entry (deterministic, PAS price)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs comparator
Comparison with platinum-based chemotherapy					
PBC	[redacted]	[redacted]			

Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	£45,693
Comparison with best supportive care					
BSC	[redacted]	[redacted]			
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	£47,463
Source: Clarification response B3 and ERG replication from company model submitted 8/2/22					

The deterministic ICERs for the company's new base case are £36,163 per QALY gained for the comparison with chemotherapy and £29,438 for the comparison with BSC. These results include all of the revisions listed in Table 7 above and the PAS price discount of [redacted] for cemiplimab. The ERG replicated the reported ICERs using the revised version of the company's model submitted with clarification questions on 8 Feb 2022. We found very small (£1) discrepancies with the reported incremental costs in the company's revised base case analyses that we could not explain, see Table 9 below for the ERG results.

Table 9 Company's revised base case results at CDF review (deterministic, PAS price)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER vs comparator
Comparison with platinum-based chemotherapy					
PBC	[redacted]	[redacted]			
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	£36,163
Comparison with best supportive care					
BSC	[redacted]	[redacted]			
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	£29,438
Source: ERG replication from company model submitted 8/2/22					

5.1.2 Probabilistic sensitivity analysis

The company report probabilistic sensitivity analysis (PSA) results in CS section A.11. For the comparison with chemotherapy (CS Table 18), the reported probabilistic ICER (£35,995) is similar to the deterministic result (£36,163). For the comparison with BSC (CS Table 19), the probabilistic ICER (£26,211) is somewhat lower than the deterministic ICER (£29,438).

The ERG re-ran the PSA and obtained ICERs that were very similar to the deterministic ICERs: £36,246 per QALY for the comparison with chemotherapy and £30,688 per QALY compared with best supportive care.

5.1.3 Deterministic sensitivity analysis

One-way deterministic sensitivity analyses are reported in tornado plots (CS Figures 21 and 22). These suggest that the ICERs are most sensitive to changes in monthly costs pre and post progression for cemiplimab, and to OS parameters for cemiplimab and the comparator.

The company's scenario analyses are reported in CS Table 20. They provided a revised version of this table in response to clarification question B3, correcting an error in Scenario analysis 1 (comparator OS based on Jarkowski data). They also provided an Excel file listing the inputs required to re-run their scenarios.

The ERG replicated the company's scenario ICERs, but with some small discrepancies that we could not explain (see scenarios 4, 5 and 6 in Table 10 below, and discussion of ERG model verification procedures in section 5.2.1). We consider that the company have provided limited justification (i) for their choice of scenario analyses and (ii) that other plausible scenarios would not have a more substantial impact on the cost-effectiveness results. See sections 6.1 and 6.2 below for additional ERG analysis.

Table 10 Company scenario analyses (deterministic, PAS price)

Scenario	Company ICERs		ERG ICER replication	
	PBC	BSC	PBC	BSC
Analysis at CDF entry	£45,693	£47,463	£45,693	£47,463
Company base case	£36,163	£29,438	£36,163	£29,438
1) Comparator survival: Jarkowski OS (Gompertz) and PFS (Weibull)	£36,446	£39,340	£36,446	£39,340
2) Population adjustment: ATC model 1	£39,346	NA	£39,346	NA
3) Population adjustment: ATT full model	£36,621	NA	£36,621	NA
4) SACT baseline characteristics: mean age 77 years, 74% male	£37,775	£30,953	£37,775	***£30,952***
5) No waning of treatment benefit	£26,263	£24,663	£26,263	***£24,662***
6) Waning between 60 and 96 months	£32,466	£26,002	***£32,465***	***£26,001***

Source: Clarification response B3 Table 20 and ERG analysis of company's model (dated 8/2/22)

5.2 Model validation and face validity check

5.2.1 Model verification procedures

The ERG conducted a range of manual checks to verify model inputs, calculations, and outputs ('white box' tests) on the company model submitted on 17th January 2022:

- Checking parameter inputs against values in the CS, excel model and cited sources.
- Checking all model outputs against results cited in the CS, including the base case, PSA and DSA and company's scenarios.
- Checking the calculations within the model engines (Arm 1, Arm 2 and Arm 3) sheets
- Running a range of tests by changing the input parameters and checking if results are plausible ('black box' tests)

Due to time constraints, we could not repeat all of the above checks on the revised company model that was received on 8th February 2022 as response to clarification question B1. We did complete the following tests on this model version:

- Reproducing the results from the CDF entry model (with starting base ICERs of £45,693 versus chemotherapy and £47,463 versus BSC) that was used as the basis for this submission.
- Re-running all of the company's scenarios and sensitivity analyses.

We noted a few minor inconsistencies in reporting of adverse events costs: i) cost of infection is reported as £256.62, ERG views this cost should be £251; and ii) cost of thrombocytopenia is reported as £655, we view the NHS reference cost is £618.28). However, these differences are unlikely to affect the cost effectiveness results.

The company submitted an Excel file with their response to clarification question B3 which listed the model settings for their base case and scenario analyses. The ERG re-ran the model with the assumptions cited in the document and found a few minor inconsistencies that we could not explain: the incremental costs for the revised base case (Table 9); and ICERs for scenarios 4-6 (Table 10).

5.2.2 Validation against SACT data

To demonstrate the generalisability of the company trials data, the Terms of Engagement for the CDF review stated that the company should compare the updated results with the data collected through the Systematic Anti-Cancer Therapy (SACT) dataset.[4] See section 3.1.3 above and CS section A.6.5 for discussion of differences between the patient population treated with cemiplimab in the company's trials and the SACT dataset.

The company report a scenario analysis with baseline demographics for the SACT population (see Table 10 above). This scenario adjusts for the older population, but it does not account for other differences between the SACT and trial populations. Clinical opinion is that 'a large proportion' of SACT patients would have received BSC rather than chemotherapy if they had not had access to cemiplimab (as they would not have been able to tolerate side effects of chemotherapy).

The company did not include the SACT data within the economic model or provide any direct validation of trial or modelled survival outcomes against the SACT results. Inspection of the SACT KM survival curve (CS Figure 7) and KM and fitted extrapolation from the company's trials (CS Figure 12) shows that mortality was higher in SACT (see Figure 1 below). This suggests that results from the company's model may not be generalisable to outcomes with cemiplimab in routine NHS use, although we note that the recruitment and outcomes of SACT might have been affected by the onset of COVID 8 months after the entry of cemiplimab into the CDF.

Figure 1: Comparison of the SACT KM curve with the company's KM and fitted OS for cemiplimab

(a) KM curve for cemiplimab from the SACT database

(b) KM curve and fitted OS curve for cemiplimab from the company model

5.2.3 Comparison with survival data from other studies

The company did not provide any comparisons of the extrapolated OS estimates with external data for the population of interest under current treatment. In Table 11 below, we compare the company's survival estimates for chemotherapy with three studies:

- Hillen et al.[23] - a retrospective analysis of 24 German and Austrian patients with median age of 76 years and advanced SCC that comprised metastatic- and locally advanced SCC;
- Amaral et al.[24] - a retrospective study of real world data of 195 German patients with advanced cutaneous squamous cell carcinoma, with a median age of 78 years; and
- Cowey et al.[25] - another a retrospective, observational study of 82 patients in US with unresectable locally advanced CSCC or metastatic CSCC).

We note that the company's OS estimates are within the highest and lowest range of survival estimates as reported in these studies.

Table 11 Comparison of OS estimates for chemotherapy

Study		OS estimates				
		1-year	*2-year*	*3-year*	*5-year*	*10-year*
Company's extrapolations		65%	38%	25%	12%	4%
Hillen et al. (DeCOG study)	Advanced SCC	87%	69%	55%	NR	NR
	Locally advanced SCC	92%	77%	71%	NR	NR
	Metastatic SCC	84%	64%	47%	NR	NR
Amaral et al.		72.9%	58.2%	51.8%	NR	NR
Cowey et al.	Overall	56.1%	30.2%	15.6%	NR	NR
	Locally advanced CSCC	61.1%	32.6%	32.6%	NR	NR
	Metastatic CSCC	54.8%	30.2%	30.2%	NR	NR

Table 12 provides OS estimates for cemiplimab from the company's base case extrapolation, compared with observed survival from the SACT dataset and the study by Strippoli et al.[4 7] The latter is a retrospective cohort of 30 Italian patients with a median age of 81 years, of whom 25 had locally advanced CSCC and the remaining 5 patients had metastatic CSCC. We note that the company's survival estimates in the first two years are significantly higher than those reported from the SACT dataset and Strippoli et al.

Table 12 Comparison of OS estimates for cemiplimab

Study	OS estimates				
	1-year	*2-year*	*3-year*	*5-year*	*10-year*
Company's extrapolations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SACT database[1]	62.5%	45%	NR	NR	NR
Strippoli et al.[2]	68%	45%	NR	NR	NR

[1]Estimates for the SACT database are approximates based on the KM curve in CS Figure 7 that shows the KM survival plot for patients receiving cemiplimab in the SACT database cohort (N=352)
[2]Estimates from Strippoli et al. are approximates based on the KM curve in Figure 4(B) in the study.

Finally, we compare the company's OS estimates for BSC (extrapolated from the Sun et al. cohort)[3] with outcomes from the study by Amaral et al.[24] This shows large differences in predicted mortality from these sources.

Table 13 Comparison of OS estimates for BSC

Study	OS estimates				
	1-year	*2-year*	*3-year*	*5-year*	*10-year*
Company's extrapolations	65%	38%	25%	13%	5%
Amaral et al.[1]	75%	65%	50%	NR	NR
[1]Estimates are approximates based on the KM curve in CS Figure 1 (f) in the study					

ERG conclusions

- ERG model checks did not identify any errors or inconsistencies that would have a material impact on the cost-effectiveness results.
- The company did not provide validation against SACT outcomes as requested in the terms of engagement for the CDF review. Observed survival with cemiplimab from the SACT dataset was evidently worse than in the company's trials and modelled extrapolations. Whilst the dataset is immature and could have been impacted by the COVID pandemic, we consider that the population is likely to be more relevant to future real-life use of cemiplimab than the population in the clinical trials. This view is supported by the similar survival results from SACT and the Italian cohort reported by Strippoli et al.[7]
- We therefore prefer company's scenario with baseline demographics from the SACT dataset. However, we note that this does not account for other differences that could affect prognosis, such as fitness and prior treatment.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

We present a summary of our additional scenario analyses in Table 14.

Table 14 Additional scenarios conducted by the ERG

Issue	***Company analyses***	***ERG analyses***
Patient characteristics- age and gender	Base case: • Age: 71.16 years • Gender: 83.1% Scenario: • Age: 77 years • Gender: 74%	Age: • 75 years (Cowe et al.), • 76 years (Hillen et al.), • 81 years (Strippoli et al.) Gender: • 85.4% (Cowe et al.), • 67% (Hillen et al.), • 80% (Strippoli et al.)
Treatment waning scenario	Base case: • 5 years Scenario: • No waning • Waning between 5 years and 8 years	• Waning at 42 months (3.5 years) • Waning at 48 months (4 years)
Efficacy- IPW analysis for the comparators	Base case: • ATT model 1, STC Scenario: • ATC model 1, ATT full model • None	• ATC full model, No IPW adjustment
Extrapolation of OS	Base case: • Cemiplimab: Lognormal • Chemotherapy: Log-logistic • BSC: Log-logistic Scenario: • Cemiplimab: None • Chemotherapy: Gompertz, log-logistic • BSC: Gompertz, log-logistic	• Cemiplimab: Weibull, Second order P(1, -0.5), log-logistic, Second order P(0, -1), Gompertz • Comparator: Weibull, Second order P(0, -1), lognormal, gompertz

Issue	*Company analyses*	*ERG analyses*
Extrapolation of PFS	Base case: • Cemiplimab: Second order • Chemotherapy: Weibull • BSC: N/A Scenario: • Cemiplimab: None • Chemotherapy: None • BSC: N/A	• Cemiplimab: loglogistic, lognormal, Weibull • Chemotherapy: Gompertz, lognormal, loglogistic, second order P(0, -0.5), second order P(0, -1) • BSC: N/A
PFS for comparators	No adjustment of data from different sources	• Chemotherapy: Adjust PFS by taking the ratio of PFS over OS from Jarkowski et al and apply the ratio to the chart review data. • BSC: Adjust PFS by taking the ratio of PFS over OS from Jarkowski et al and apply the ratio to the Sun et al.

6.2 Impact on the ICER of additional ERG analyses

We present the cost-effectiveness results of the ERG additional scenarios in Table 15 below. The results of the ERG additional scenarios indicated that the ICER for cemiplimab versus chemotherapy ranged between £33,195 (Scenario: PFS for chemotherapy extrapolated using Gompertz) and £43,233 (Scenario: Treatment waning at 42 months). For cemiplimab versus BSC, the ICER ranged between £32,646 (Scenario: Patient demographic with mean age of 81 years and 80% male, based on the population in an Italian cemiplimab cohort reported by Strippoli et al.[7]) and £28,859 (Scenario: without applying population adjusted indirect comparison for efficacy).

Table 15: Additional analyses undertaken by the ERG (PAS price)

Assumption		***ICER vs PBC***	***ICER vs BSC***
Company base case		£36,163	£29,438
Patient characteristics	Age:75 years; Gender ratio: 85.4% male (Cowe et al.)	£36,828	£30,129
	Age:76 years; Gender ratio: 67% male (Hillen et al.)	£37,417	£30,621
	Age: 81 years; Gender ratio: 80% male (Strippoli et al.)	£40,004	£32,646
Treatment waning	Switch to comparator hazard at 48 months (n=[redacted] at risk)	£40,160	£30,775
	Switch to comparator hazard at 42 months (n=[redacted] at risk)	£43,233	£31,676
Efficacy- Population adjustment	ATC full model	£39,191	NA
	None (no IPW or STC)	£36,814	£28,859
OS extrapolation: cemiplimab	Weibull	£36,089	£29,309
	Second order P(1,-0.5)	£35,834	£29,352
	Log-logistic	£36,354	£29,380
	Second order P(0,-1)	£36,132	£29,452
	Gompertz	£35,784	£29,357
OS extrapolation: comparator	Weibull	£43,186	£29,735
	Second order P(0, -1)	£35,652	£29,919
	Lognormal	£38,124	£29,511
	Gompertz	£35,566	£29,871
PFS extrapolation: cemiplimab	Log-logistic	£37,942	£30,574
	Lognormal	£37,998	£30,614
	Weibull	£39,512	£31,609
PFS extrapolation: chemotherapy	Gompertz	£33,195	NA
	Lognormal	£34,560	NA
	Loglogistic	£33,791	NA
	Second order P(0, -0.5)	£33,396	NA
	Second order P(0, -1)	£34,043	NA
PFS adjustment: comparators	Taking the ratio of PFS over OS from Jarkowski et al and applying it to the CHART review data (chemotherapy) and Sun et al (BSC)	£36,852	£31,512

Source: produced by ERG from company's model (dated 08/02/22)
Abbreviations: BSC best supportive care; PBC platinum based chemotherapy; OS overall survival; PFS progression free survival; NA not applicable; ICER incremental cost-effectiveness ratio; PAS patient access scheme

6.3 ERG's preferred assumptions

As discussed in Section 5.2.2, the ERG views the SACT cohort to reflect the patients treated with cemiplimab in UK NHS practice. We present the results of the ERG preferred assumption in Table 16. This increases the ICER of cemiplimab versus chemotherapy to £37,775 (an increase of £1,612 from the company's base case) and that of cemiplimab versus BSC to £30,952 (an increase of £1,514 from the company's base case). We also conduct a range of scenarios on the ERG preferred analysis, presented in Table 17 below

Table 16 ERG preferred analysis (PAS price)

Assumption	***ICER vs PBC***	***ICER vs BSC***
Company base case	£36,163	£29,438
+ Population characteristics from SACT (age: 77 years; 74% male)	£37,775	£30,952
ERG preferred analysis	£37,775	£30,952
Abbreviations: BSC best supportive care; PBC platinum-based chemotherapy; O; ICER incremental cost-effectiveness ratio; PAS patient access scheme		

Table 17 Additional scenarios conducted on the ERG preferred assumption (PAS price)

Assumption	***ICER vs PBC***	***ICER vs BSC***
ERG preferred assumption	£37,775	£30,952
Treatment waning: 48 months	£41,935	£32,380
Treatment waning: Between 60 months and 96 months	£33,942	£27,475
Efficacy- population adjustment: ATC full model	£40,863	-
Efficacy- population adjustment: ATC model 1	£41,021	-
Efficacy- population adjustment: ATT full model	£38,531	-
OS extrapolation for cemiplimab: Weibull	£37,675	£30,793
OS extrapolation for cemiplimab: Second order P(1, -0.5)	£37,503	£30,838
OS extrapolation for cemiplimab: Loglogistic	£37,969	£30,879
OS extrapolation for cemiplimab: Second order P(0, -1)	£37,749	£30,960
OS extrapolation for cemiplimab: Gompertz	£37,412	£30,843
OS extrapolation for comparator: Weibull	£44,379	£31,351
OS extrapolation for comparator: Second order P(0, -1)	£37,627	£31,443
OS extrapolation for comparator: Lognormal	£39,530	£31,069
PFS adjustment for comparators	£38,414	£33,246
Abbreviations: BSC best supportive care; PBC platinum-based chemotherapy; O; ICER incremental cost-effectiveness ratio; PAS patient access scheme		

6.4 Conclusions of the cost effectiveness section

Extended trial data

- The extended follow up data now available from the company's trials has provided better evidence for the survival extrapolations used for cemiplimab in the economic model, and greater confidence that they will be maintained for longer.
- Clinical experts consulted by the ERG reported a good experience of using cemiplimab under the CDF. They expressed enthusiasm over the responses that they had observed and confidence in use of the treatment for a wider group of patients, including some who would not be offered, or who would decline, treatment with platinum base chemotherapy due to concerns over adverse effects.
- The SACT dataset has demonstrated that within the CDF, a wider group of patients have been treated with cemiplimab than in the company's trials, including patients who are older, less fit and with a degree of immune compromise. This is positive, but it adds to uncertainty over the generalisability of the company's trial data to the population who would be treated with cemiplimab in UK practice.
- This suggests that the OS and PFS extrapolations in the company's economic model are likely to be more favourable than one would expect in routine NHS practice.

Comparator data and indirect comparisons

- A high degree of uncertainty remains over survival extrapolations for chemotherapy and best supportive care due to continuing weakness in the evidence base for these comparators, and the lack of data to support adequate population adjustment for the unanchored indirect comparisons with the cemiplimab trial data.
- There is particularly sparse data for best supportive care, as only patients who had received chemotherapy were included in the final UK chart review dataset; and the Sun cohort is very limited.
- Data on progression free survival is also sparse, as the company do not consider the chart review data on progression to be reliable, and this outcome was not reported for the Sun cohort. The company therefore rely on different sources to model the survival parameters for the chemotherapy comparator: the chart review for OS and the Jarkowski study for PFS, and they assume that all patients on best supportive care start in the 'post-progression' health state.

Treatment duration and persistence of effects

- The model reflects the TA592 recommendation that cemiplimab treatment should continue for 24 months or disease progression, whichever is sooner. However, the model assumes that no patients stop treatment prior to disease progression, which does not reflect experience from the SACT cohort. This suggests that the cost of cemiplimab may be overestimated, and ICERs underestimated.
- The company's approach to modelling waning of the relative treatment benefit for cemiplimab is consistent with that in TA592. They have assumed a longer persistence of the advantage in their updated base case (5 rather than 3 years), based on extended data from EMPOWER. Although 5 years is the maximum duration of follow up currently available, the assumption of an instantaneous loss of a relative survival advantage at this time is probably conservative.

Summary of cost-effectiveness results

- The company's revised base case ICER for the comparison with chemotherapy is above £36,163 per QALY gained and remains above £30,000 per QALY in all of their scenarios, except with the assumption of no waning of treatment effects.
- Their base case ICER for the comparison with best supportive care is £29,438 per QALY gained. This rises above £30,000 per QALY when OS and PFS extrapolations are based on data form the Jarkowski cohort (as in the TA592 analysis), or when the initial age of patients at treatment initiation is based on that in the SACT cohort.
- We conducted additional scenario analyses to test a wider range of uncertainties. Our preferred scenario includes the SACT patient demographics (77 years, 74% male). With this assumption all of our scenarios for the comparison with chemotherapy were above £30,000 per QALY. For the comparison with best supportive care, the ICER was below £30,000 with a less conservative waning assumption (gradual loss of the relative benefit between 5 and 8 years), but above this threshold for all other scenarios that we tested.

7 END OF LIFE

The CS argues that cemiplimab meets the NICE end-of-life criteria. They summarise their justification for reaching this conclusion in CS Table 21. Our critique of the company's argument is summarised in Table 18 below.

Whilst the company's analysis confirms that cemiplimab offers an extension of life exceeding 3 months when compared to chemotherapy or BSC, their base case analysis indicates that patients receiving chemotherapy have a longer life expectancy, more than 24 months. Those receiving BSC have a life expectancy shorter than 24 months. This indicates that end of life criteria is only met for patients receiving BSC, and not chemotherapy.

The ERG's preferred analysis (including age and gender based on the SACT dataset) confirms that cemiplimab offers an extension of life which exceeds 3 months when compared to chemotherapy or BSC (gains of 3.61 life years and 5.19 life years respectively). This analysis also indicates that patients receiving chemotherapy have a life expectancy longer than 24 months (2.65 life years or 31.8 months) but that those receiving BSC have a life expectancy shorter than 24 months (1.42 life years or 17.04 months). This suggests that end-of-life criteria are met for patients receiving BSC, and not chemotherapy.

We also note that there is additional uncertainty over whether cemiplimab meets end-of-life criteria because of questions over the generalisability of the cemiplimab and comparator data to the population who would be treated with cemiplimab in routine practice. This is particularly true for BSC, as data for this group is very sparse, as patients treated with BSC were excluded from the UK chart review and the Sun cohort is limited.

Table 18: End-of-life criteria

Criterion	Company's statement	ERG critique
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The company argue that without cemiplimab patients have a life expectancy less than 24 months. For chemotherapy, they report that median survival was estimated to be ~ 15 months by both the UK chart review and the Jarkowski 2016. Furthermore, they state that	In the company's base case economic model, the mean OS for patients receiving chemotherapy was 2.72 life years (32.64 months) using the retrospective chart review which increases to 2.80 life years (33.6 months) when using the data from Jarkowski et al.

	clinicians they consulted agreed that patients receiving chemotherapy are not expected to survive beyond 2 years. For those receiving BSC, they argue that patients are not expected to survive longer than 6 months and median survival reported by Sun et al was 5 months.[26]	For patients receiving BSC, the mean OS using the study by Sun et al. was 1.46 Life years (17.52 months) which increased to 2.80 Life years (33.6 months) using the data from Jarkowski et al. No discounting was applied to obtain these estimates.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The company argue that cemiplimab offers a substantial extension to life for advanced CSCC patients with survival of [redacted] at [redacted] years. The company state that UK clinical experts support their statement that cemiplimab offers a greater than 3-month extension to life for this patient population. This is further supported by the SACT database that supports an extension to life of greater than 3 months.	In the base case economic modelling, cemiplimab is associated with an incremental gain of 3.0 life-years (36 months) compared to chemotherapy and 4.55 life-years (54.6 months) compared to BSC, when costs and QALYs are discounted at 3.5% pa. With no discounting, cemiplimab is associated with a gain of 3.85 life-years (46.2 months) compared to chemotherapy and 5.89 life-years (70.7 months) compared to BSC respectively.

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Appendix 1

Company responses to the NICE Committee's preferred assumptions as stated in the Terms of Engagement

Assumption	Terms of engagement	Addressed by the company submission	Rationale if different	ERG comments
Population	Adults with metastatic or locally advanced cutaneous cell carcinoma that is not appropriate for curative surgery or curative radiotherapy are the relevant population for the CDF review. During technical engagement it was agreed that people with significant autoimmune disease or who have had a solid organ transplant are unlikely to be eligible for treatment.	**Yes** Study populations in all the new evidence match the population stated in the Terms of Engagement. However, there is uncertainty around the rationale for excluding some patients from the company's chart review, i.e. whether some patients relevant to the scope may have been excluded.	Not applicable	The company suggest that people with autoimmune diseases or who have had a solid organ transplant may benefit from cemiplimab (CS Table 1). The SACT dataset,[4] other real-world cohorts,[5-8] and one of the ERG's clinical experts confirmed that some people with autoimmunity or a solid organ transplant have received cemiplimab but numbers were small.
Comparators	The company should present clinical and cost-effective evidence for cemiplimab compared to chemotherapy and best supportive care.	**Yes** Note that chemotherapy is limited to platinum-based chemotherapy (PBC), which is consistent with TA592.	Not applicable	Due to the toxicity of chemotherapy and growing experience of the tolerability of cemiplimab, BSC is becoming the most relevant comparator to cemiplimab. However, BSC evidence is difficult to identify. [1 2]

Generalisability of trial evidence	The company should use data collected through SACT to demonstrate the generalisability of the trial data.	**Yes, with limitations** The company have considered the SACT data. This indicated differences between the population treated with cemiplimab in NHS practice and the trial populations, although these data were collected during the COVID-19 pandemic which would likely influence generalisability.	Not applicable	SACT does not report dosing regimens but according to the stated cycle length the licensed flat dose appears to have been used. Limited baseline characteristics were collected in SACT.
Survival outcomes	The company should use updated survival data from EMPOWER-CSCC 1 and fully explore the most appropriate method to extrapolate survival outcomes. Data collected through SACT should be used to validate the trial outcomes.	**Partly** The latest data cuts for the company trials (July 2021 for EMPOWER-CSCC 1 and 2019 for Study 1423) were pooled and used to inform PFS and OS. Extrapolation methods are explored in the CS based on model fit and clinical opinion. However, SACT data have not been used to validate the company trial survival outcomes.	The rationale for not using SACT data to validate the survival outcomes is not explicitly justified in the CS. The company state that "Data from SACT is short term, in some instances incomplete and contains a number of uncertainties compared to EMPOWER-CSCC 1, therefore use of the longer-term trial data is preferred" (CS section A.6.5).	Although follow up in SACT was shorter than in the company trials, median OS was reached. The CS is not explicit about the "incomplete" and "uncertain" aspects of the SACT data being referred to. Company trial survival extrapolations are reported in CS Table 15 and CS sections A.15.2 to A.15.4. Extrapolations used in the economic model are reported in CS section A.9.
Comparator data	The company should use their UK chart review and any additional data that has become available during the period of managed	**Yes, with limitations** The company use three comparator cohorts:	Not applicable	The company raised concerns about reliability of the data originally collected in the chart review. The ERG's clinical

	access to inform the comparator arms.	• Company chart review: OS for platinum-based chemotherapy. • Jarkowski et al. study (not new): OS & PFS for platinum-based chemotherapy. • Sun et al. study: OS for best supportive care However, reliability of the company's chart review is uncertain.		experts also questioned the appropriateness of eligibility criteria that were applied to the chart review data post-hoc. The ERG and clinical experts did not identify any new studies that were not included by the company.
Relative effectiveness	The company should fully explore the most appropriate treatment comparison method and utilize any updated data that has become available during the period of managed access. The committee concluded that the relative effectiveness estimates for cemiplimab are highly uncertain regardless of ITC method as all used unreliable comparator data.	**Yes, with limitations** The company have used updated cemiplimab and comparator data to compare cemiplimab against chemotherapy and BSC using three adjusted ITC methods (IPW, STC, MAIC). However, high uncertainty remains due to limitations in the comparator data. The proportional hazards assumption is not supported so hazard ratios are illustrative only.	Not applicable	Hazard ratios are not required in the economic model, which is informed by separate ITC-adjusted survival curves (consistent with the approach in TA592). The ERG were not provided with the individual participant data so could not verify that company analyses were conducted as described in the CS and clarification responses.
Treatment effect duration	The company should use updated survival data from EMPOWER-CSCC 1 and fully explore the	**Yes** The company have used the updated survival data from EMPOWER-CSCC 1	Not applicable	Not applicable

	impact of a 24-month stopping rule on long-term outcomes.	and explored the impact of a 24-month stopping rule on long-term outcomes.		
Most plausible ICER	The committee agreed that cemiplimab demonstrated plausible potential to be cost-effective. Due to uncertainty in the evidence base, the committee did not state a preferred ICER	Not applicable	Not applicable	Not applicable
End of life	The company should demonstrate whether cemiplimab meets the end-of-life criteria	**Yes** The company argue that cemiplimab meets end-of-life criteria compared to both chemotherapy and BSC. However, their base case model indicates that the criteria are met for the comparison with BSC, but not for the comparison with chemotherapy (as the life expectancy exceeds 2 years. The ERG preferred scenario reiterates this conclusion.	Not applicable	Overall, it remains unclear if cemiplimab meets end-of-life criteria due to high uncertainty in the comparator data.
BSC: best supportive care; IPW: inverse probability weighting MAIC: matched adjusted indirect comparison; OS: overall survival; PBC: platinum-based chemotherapy; PFS: progression free survival; SACT: Systemic Anti-Cancer Therapy dataset; STC: simulated treatment comparison				

Appendix 2

Nine potentially relevant studies, published in full since November 2018, were identified by the ERG. However, two reviewers excluded them all from this review. The studies and the reason for exclusion are summarised in the table below.

Real-world studies of treatments for advanced CSCC identified and excluded by the ERG

Reference	Setting; design	Population	Intervention	Outcomes	Reason for exclusion
Amaral et al 2019[24]	Germany; retrospective	N=50 (195 total advanced CSCC, 50/195 inoperable); median age 78 years; ECOG PS not reported	Chemotherapy 20/50; BSC 12/50	Overall survival	Outcomes not reported for population subgroups relevant to this review.
Baggi et al 2021[5]	Italy; multicentre (17), retrospective	N=131 (91 laCSCC, 40 mCSCC, 9.2% had autoimmune disease); median age 79 years; ECOG PS 0-1 in 77.9% of 125/131	Cemiplimab	Treatment related adverse events; response rates	Outcomes. OS and PFS not reported.
Chapalain et al 2020[27]	France; single centre, retrospective	N=42 (stage IV CSCC, 31% immunocompromised); median age 75.5 years; ECOG PS 0-1 in 93%	Chemotherapy and/or cetuximab	OS at 4 years; response rate; adverse events	Only 6/42 received chemotherapy alone at 1L, and 20/25 at 2L. Outcomes not reported for population subgroup relevant to this review.

Cowey et al 2020[25]	United States; retrospective, observational	N=82 (17 laCSCC, 65 mCSCC); median age 75 years; ECOG PS 0 in 10%, 1 in 88%, not reported in 2%	Most common 1L regimens: Carboplatin + paclitaxel (27%); Cetuximab monotherapy (24%)	OS	Outcomes not reported for population subgroup relevant to this review (i.e. carboplatin + paclitaxel).
Hillen et al 2018[23]	Germany and Austria; multicentre (24), retrospective	N=190 (76 laCSCC, 114 mCSCC, 24% immunocompromised); median age 78 years; ECOG PS 0-1 in "most"	Chemotherapy including PBC.	Response rates	Outcomes. PFS and OS not reported.
Hober et al 2021[6]	France; multicentre (58), retrospective	N=245 (24% immunocompromised); mean age 77 years; ECOG PS >= 2 in 27%	Cemiplimab	Response rate; OS at 1 year; PFS	Population. Includes immunocompromised and ECOG 2 or greater.
Kramb et al 2021[28]	Germany; single centre, retrospective	N=59 (laCSCC unresectable 20/59, mCSCC unresectable 25/59, immunocompromised were excluded); median age 76 years; ECOG PS not reported	15/45 unresectable patients received systemic treatment	Response rates; PFS; OS	Outcomes not reported for population subgroup relevant to this review (i.e. any of the PBC regimes).

Strippoli et al 2021[7]	Italy; single centre, retrospective	N=30 (25 laCSCC, 5 mCSCC, 5/30 immunocompromised); median age 81 years; ECOG PS 0 in 23%, 1 in 57%, 2 in 20%	Cemiplimab	Response rate; adverse events; OS; PFS	Population. Older, ECOG PS 2.
Valentin et al 2021[8]	France; single centre, retrospective	N=22 (laCSCC and mCSCC); median age 83 years; ECOG PS 0 or 1 in 73%	Cemiplimab	Safety in daily practice – AEs and SAEs	Outcomes. OS and PFS not reported.
ECOG PS: Eastern Cooperative Oncology Group Performance Status scale; laCSCC: local advanced cutaneous squamous cell carcinoma; mCSCC metastatic cutaneous squamous cell carcinoma; OS: overall survival; PBC: platinum-based chemotherapy; PFS: progression free survival					

Appendix 3

Reproduction of CS Table 23 (Summary of baseline patient characteristics for main data sources) with corrections by ERG and including the Named Patient Scheme study for comparison

Red data indicate corrections made by ERG		Cemiplimab					BSC	Chemotherapy	
		EMPOWER-CSCC-1	**Study 1423**	**Pooled company trials**	**SACT dataset (CDF)**	**Named Patient Scheme study**	**Sun et al, 2019**	**Chart review (cohort for analysis),**	**Jarkowksi et al, 2016**
N		193	26	219	352	38	32	[redacted]	25
Disease severity	laCSCC mCSCC	78 (40.4) 115 (59.6)	10 (38.5) 16 (61.5)	88 (40.2) 131 (59.8)	172 (49) 180 (51)	10 (26.4) 28 (73.6) [a]	12 (42.9) [b, c] 16 (57.1) [b, d]	[redacted]	19 (76) [f] 6 (24) [f]
Age median (range)		72 (38-96)	72.5 (52-88)	72 (38-96)	77	74 (28-90)	73 (43-89)	[redacted]	66.4
Gender n (%)	Male	161 (83.4)	21 (80.8)	182 (83.1)	262 (74)	31 (81.6)	26 (81.3)	[redacted]	18 (72)
Differen-tiation n (%)	Well Undiff. [g] Undetermined	[redacted]	2 (7.7) 17 (65.4) 7 (26.9)	[redacted]	- - -	- - -	-	[redacted]	-
Tumour location n (%)	Head and neck Trunk Extremities	[redacted]	19 (73.1) 2 (7.7) 5 (19.2)	[redacted]	- - -	24 (63.2) - -	32 (100) 0 (0) 0 (0)	[redacted]	11(44.0) 7 (28.0) 3 (12.0)
T stage n (%) [h]	T0 Tis Tx T1 T2 T3 T4	[redacted]	- - 8 (30.8) 3 (11.5) 10 (38.5) 2 (7.7) 3 (11.5)	[redacted]	- - - - - - -	- - - - - - -	8 (25.0) T1/T2: 11 (34.4)	[redacted]	- - - - - - -

		[redacted]		[redacted]			T3/T4: 13 (40.6)	[redacted]	
ECOG PS n (%)	0 1 2	86 (44.6) 107 (55.4) -	10 (38.5) 16 (61.5) -	96 (43.8) 123 (56.2)	64 (18) 223 (63) 14 (4) 51 missing	0-1: 33 (86.8)	0-2: 32 (100)	[redacted]	- - -
Prior systemic therapy n (%)		65 (33.7)	15 (57.7)	80 (36.5)	-	9 (23.7)	-	[redacted]	Not reported [i]
Prior radiation n (%)		[redacted]	21 (80.8)	[redacted]	-	-	32 (100)	[redacted]	-

[a] The Named Patient Scheme study distinguishes between nodal disease and distant metastases (26.4% nodal disease, 26.4% distant metastases, 21.1% had both nodal and distant disease).
[b] Data are for 28 of the 32 patients in the study who were immunocompetent; 4 patients recorded as having both locoregional and distant disease are excluded (these four patients would be classified as mCSCC according to the company's definition).
[c] Locoregional disease at 1st recurrence as defined by Sun et al. 2019 which does not correspond to laCSCC as defined by the company (see section 3.1.4.3).
[d] Distant disease at 1st recurrence as defined by Sun et al. 2019 which does not correspond to mCSCC as defined by the company (see section 3.1.4.3).
[e] According to the Chart Review Protocol patient records were included in a 60:40 mCSCC : laCSCC ratio so these proportions may not reflect real world prevalence of laCSCC and mCSCC in this study.
[f] The Jarkowski et al. 2016 paper refers to locoregional and metastatic groups but does not define these. The ERG assume that the locoregional group would overlap with mCSCC as defined by the company, since mCSCC includes regional nodal disease. However, as noted in CS Appendix D.1.3.2 in the TA592 appraisal, Jarkowski et al. use the terms 'locoregional' and 'locally advanced unresectable' interchangeably which might suggest that locoregional could be equivalent to laCSCC. But this is speculative.
[g] Reported as "Moderate/Poor/Undifferentiated" elsewhere (e.g. Chart Review Report Table 3).
[h] The T-stage indicates tumour thickness and local spread into nearby structures.
[i] The proportion who received prior systemic therapy is not reported in the Jarkowski et al. 2016 study publication; the value of 8 (32) reported in CS Table 23 appears to be for therapy received during the study. The company do not explain their interpretation of the data.

Appendix 4

Face validity issues noted by the company for their retrospective chart review

Issue (CS section A.15.6)	Company comments	ERG and clinical experts' comments	Issue resolved by the data audit?
Large data gaps for "many" patients where no events or visits were observed for the laCSCC population.	These gaps appear contrary to standard treatment patterns for patients with advanced cancers	Clarification response A10 indicates 53 patients (50%) had follow up gaps >12 months where no visits were confirmed.	No
Higher uptake of chemotherapy than would be expected.	Once patients have metastasized or progressed following surgery/ radiotherapy, there are no palliative treatments, so patients are cared for in the community (i.e. GPs) rather than in hospitals.	ERG clinical experts commented that patients with metastatic CSCC do not tend to be discharged into the community and doctors may try treatment (e.g. chemotherapy) for patients who they perceive to be fitter. A hospital chart review may be more likely to pick up these cases.	No
Lack of information on prior and palliative treatment (surgery and radiotherapy).	Few patients are recorded having prior radiotherapy, surgery, or systemic therapy. In clinical practice few patients are initially diagnosed with metastatic disease so would usually have received surgery or radiotherapy prior to diagnosis.	ERG clinical experts agreed most patients present with laCSCC before progression to mCSCC. However, the experts questioned the validity and completeness of the chart review since hospital medical records should always include information on prior treatment for CSCC.	No
Longer survival estimates than expected in 90 patients who received ≥1 line of	OS for patients who received at least one line of therapy post advanced diagnosis (n=90) were longer than estimates available in the published literature, particularly for	ERG clinical experts agreed that OS of these 90 patients in the chart review appears longer than would be expected. Some patients may have received radical radiotherapy in combination with	Yes – demonstrated by comparing CS Figure 67 (pre-audit, N=90) against Chart Review

therapy post advanced diagnosis.	laCSCC patients (CS section A.15.6; CS Figure 67). In particular, survival times of patients in laCSCC were considered high compared to clinical expectation that survival in this population would not be expected to be beyond 2 years.	chemotherapy which could lead to better outcomes. The CS does not report OS separately for laCSCC patients.	Report Figure A7 (post-audit, [redacted])
A large proportion of the chart review population were indicated to have received palliative radiation and/or palliative surgery; however, dates of administration were not recorded and may have occurred prior to, during, or following systemic treatment.	It is possible that some of these patients may have received regimens more akin to definitive rather than palliative radiotherapy, though this cannot be determined from the original data collection. Potential under-reporting of palliative treatments could have contributed to the over-estimation of survival.	ERG clinical experts commented that radiotherapy dates should be accessed easily through hospital reporting systems and hospital radiotherapy systems. Lack of these data makes the chart review harder to interpret and raises questions about its usefulness.	No
The reason for excision biopsies was not collected, but the biopsies could have been a form of tumour debulking (CS section A.6.2.1).	The company argue that if patients received tumour debulking they would be incomparable to those in the company trial (i.e. laCSCC, not eligible for surgery or radiotherapy) (CS section A.6.2.1).	ERG clinical experts disagreed with the company assumption that doctors might report an excision biopsy (curative) as tumour debulking (palliative). The experts questioned why patients treated palliatively would be “incomparable” with those in the company trial, since patients receiving BSC would be	No

		eligible for cemiplimab, and the company trials included patients with mCSCC as well as laCSCC.	
Deaths made up a significant portion of the PFS events in the chart review, despite these occurring well after cessation of therapy.	Patients would be expected to progress prior to death, especially in the metastatic cohort, suggesting progression was not formally recorded in many charts. Due to lack of reliable information on progression events PFS was not estimated (CS section A.14.2).	ERG clinical experts commented that these patients may have been discharged to the community then progression would not be recorded. If they had palliative treatment, then progression would be recorded as a reason to discontinue. The ERG agree that the apparent lack of (and possible inconsistency in) reporting progression events precludes reliable estimation of PFS.	No
Relatively few patients experienced any events within the first six months of treatment.	Substantial numbers of patients die within the first six months in the company trials, as well as in all published literature on this patient population. This period of non-events could be due to the data collection process not being sufficiently comprehensive (it may be the case that not all events were recorded) or as patients enrolled in the chart review were generally healthier.	ERG clinical experts commented that patients in the chart review may have been at an earlier stage of laCSCC, whereas substantial numbers of patients dying within the first 6 months in the company trials suggests many had distant metastases. This is where lack of detail in the chart review may explain the outcomes. Poor comprehensiveness of data collection is also plausible.	No

Appendix 5

Covariates included in the company ITC analysis models estimating the average treatment effect in the treatment group (ATT) and average treatment effect in the comparator group (ATC)

Model	Median Age	Disease severity	Differen-tiation	Sex	Tumour location	ECOG PS	Prior systemic therapy	Prior radiation	T-stage
ATT full	Y	Y	Y	Y	Y	Y	N	N	Y
ATT1	Y	Y	Y	Y	N	N	N	N	Y
ATT2	N	Y	Y	Y	N	N	N	N	Y
ATT3	Y	Y	N	Y	Y	N	N	N	Y
ATT4	Y	Y	N	Y	N	N	N	N	Y
ATT5	N	Y	Y	Y	N	N	N	N	Y
ATT6	Y	Y	Y	Y	Y	N	N	N	Y
ATT7	Y	Y	N	Y	N	N	N	N	N
ATT8	Y	Y	N	Y	Y	N	N	N	N
ATT9	N	Y	Y	N	N	N	N	N	Y
ATT10	Y	Y	Y	N	N	N	N	N	Y
ATC full	Y	Y	Y	Y	Y	Y	Y	N	Y
ATC1	Y	Y	Y	Y	Y	Y	Y	N	N
ATC2	N	Y	Y	Y	Y	Y	Y	N	N
ATC3	N	Y	Y	Y	N	Y	Y	N	N
ATC4	Y	Y	Y	N	N	Y	Y	N	N
ATC5	Y	N	Y	Y	Y	Y	N	N	N
ATC6	Y	N	Y	Y	N	Y	N	N	N
ATC7	Y	Y	Y	Y	N	Y	N	N	N
ATC8	Y	Y	Y	Y	Y	Y	N	N	N
ATC9	Y	Y	Y	Y	Y	N	N	N	N
ATC10	Y	Y	Y	Y	N	N	N	N	N

Sources: Chart Review Report Tables 5, 7, C1, D2 and Figures D18, D19, D20, D21, D22

Appendix 6

Overview of ITC model fit, data sources and hazard ratios for ITC comparisons of cemiplimab (company trials) versus chemotherapy (company chart review). All data sources refer to the company Chart Review Report.[12]

Model	Source	Covariates included	Balance [a]	ESS [b]	ESS trimmed	Comparisons of reweighted covariates; KM curves	Number (trimmed analysis) of covariates with ASD>10% after reweighting [c]		HR [d]	HR trimmed [d]
ATT full	Tables 7, C1	[redacted]	[redacted]	[redacted]	[redacted]	Tables 6, B1 KM: Figure 4	[redacted]	Figure 2	[redacted]	[redacted]
ATT1	Tables 5, 7, D3	[redacted]	[redacted]	[redacted]	[redacted]	Table B2 KM: Figure 5	[redacted]	Figure 3	[redacted]	[redacted]
ATT2	Table 7	[redacted]	[redacted]	[redacted]	[redacted]	Table B3 KM: Figure C1	[redacted]	Figure C10	[redacted]	[redacted]
ATT3	Table 7	[redacted]	[redacted]	[redacted]	[redacted]	Table B4 KM: Figure C2	[redacted]	Figure C11	[redacted]	[redacted]
ATT4	Table 7	[redacted]	[redacted]	[redacted]	[redacted]	Table B5 KM: Figure C3	[redacted]	Figure C12	[redacted]	[redacted]
ATT5	Table 7	[redacted]	[redacted]	[redacted]	[redacted]	Table B6 KM: Figure C4	[redacted]	Figure C13	[redacted]	[redacted]
ATT6	Table C1	[redacted]	[redacted]	[redacted]	[redacted]	Table B7 KM: Figure C5	[redacted]	Figure C14	[redacted]	[redacted]
ATT7	Table C1	[redacted]	[redacted]	[redacted]	[redacted]	Table B8 KM: Figure C6	[redacted]	Figure C15	[redacted]	[redacted]
ATT8	Table C1	[redacted]	[redacted]	[redacted]	[redacted]	Table B9 KM: Figure C7	[redacted]	Figure C16	[redacted]	[redacted]

ATT9	Table C1	[redacted]	[redacted]	[redacted]	[redacted]	Table B10 KM: Figure C8	[redacted]	Figure C17	[redacted]	[redacted]
ATT10	Table C1	[redacted]	[redacted]	[redacted]	[redacted]	Table B11 KM: Figure C9	[redacted]	Figure C18	[redacted]	[redacted]
ATC full	Table D2	[redacted]	[redacted]	[redacted]	[redacted]	Tables D1, D4 KM: Figure D3	[redacted]	Figure D1	[redacted]	[redacted]
ATC1	Table D2	[redacted]	[redacted]	[redacted]	[redacted]	Tables 5, D5 [e] KM: Figure D4	[redacted]	Figure D2	[redacted]	[redacted]
ATC2	Table D2	[redacted]	[redacted]	[redacted]	[redacted]	Table D6 KM: Figure D5	[redacted]	Figure D14	[redacted]	[redacted]
ATC3	Table D2	[redacted]	[redacted]	[redacted]	[redacted]	Table D7 KM: Figure D6	[redacted]	Figure D15	[redacted]	[redacted]
ATC4	Table D2	[redacted]	[redacted]	[redacted]	[redacted]	Table D8 KM: Figure D7	[redacted]	Figure D16	[redacted]	[redacted]
ATC5	Table D2	[redacted]	[redacted]	[redacted]	[redacted]	Table D9 KM: Figure D8	[redacted]	Figure D17	[redacted]	[redacted]
ATC6	Figure D18	[redacted]	[redacted]	[redacted]	[redacted]	Table D10 KM: Figure D9	[redacted]	Figure D18	Not reported	Not reported
ATC7	Figure D19	[redacted]	[redacted]	[redacted]	[redacted]	Table D11 KM: Figure D10	[redacted]	Figure D19	Not reported	Not reported
ATC8	Figure D20	[redacted]	[redacted]	[redacted]	[redacted]	Table D12 KM: Figure D11	[redacted]	Figure D20	Not reported	Not reported
ATC9	Figure D21	[redacted]	[redacted]	[redacted]	[redacted]	Table D13 KM: Figure D12	[redacted]	Figure D21	Not reported	Not reported
ATC10	Figure D22	[redacted]	[redacted]	[redacted]	[redacted]	Table D14 KM: Figure D13	[redacted]	Figure D22	Not reported	Not reported
Sensitivity analyses basing ATC model on the best fitting ATT model										

ATC / full ATT model	Table D3	[redacted]	[redacted]	[redacted]	[redacted]	Not reported	Not reported	Not reported	[redacted]	[redacted]
ATC / ATT1 model	Table D3	[redacted]	[redacted]	[redacted]	[redacted]	Not reported	Not reported	Not reported	[redacted]	[redacted]

[a] Higher values indicate greater balance of covariates between the studies

[b] Effective sample size

[c] The number of covariates with an absolute standardised difference (ASD) of >10% between studies after reweighting. Numbers in brackets are for the trimmed analysis. These data were obtained by visually inspecting the source Figures listed. The company report these data numerically only for the ATT full model (the absolute standardized difference was >10% for 5 matching variables) and for ATT model 1 (the standardized mean difference was less than 10% for five of the seven prognostic factors) (Chart Review Report section 4.2.1). The visual observations are more conservative towards detecting the stronger deviations, as they cannot resolve very small differences close to 10%.The data in this column show that for all models at least two covariates had a standardised mean difference >10%, indicative of incomplete balancing of covariates in all models.

[d] Hazard ratios are uncertain and should be interpreted with caution as the assumption of proportional hazards was violated.

[e] Mislabelled Table D4 in the Chart Review Report.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592) [ID3833]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 24 February 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 SACT dataset availability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Some aspects of the report suggest that further exploration with the SACT data was possible. However, the company only received the final version of the report from NHS Digital at the end of November 2021 and the Company does not have access to the IPD. Page 4: "*The company use the SACT data only in a limited way to validate outcomes of the cemiplimab trials.*" Page 13: "*Whilst the SACT data do inform the economic analysis, this is as a scenario representing only two SACT covariates (age and gender)*" Page 19: "*The company explored the impact of the SACT population characteristics as a scenario analysis in their economic model, although this was limited to two covariates (age and gender)*"	Please amend text to note that it has been acknowledged that analyses using SACT data were limited due to the availability of the IPD, which is owned by NHS Digital and not available to Sanofi.	The current text could suggest that the company are purposely avoiding providing additional analyses using SACT data.	We acknowledge limitations of the SACT data. However, these should not have prevented use of digitised SACT KM results for validation purposes. Page 4: We have amended the text in the "SACT dataset" bullet as follows: "*However, relatively limited population characteristics are available for the SACT dataset, and generalisability of the findings may be influenced by the COVID-19 pandemic. The company use the SACT data only in a limited way to validate outcomes of the cemiplimab trials, as they did not digitise the SACT overall survival KM data or comparison against results from the company's trials and modelled extrapolations.*" We also note that our use of the term 'covariates' in relation

			to the company's scenario analysis with SACT baseline characteristics (CS Table 20) is potentially misleading, as the age and gender inputs to the model do not modify the ITC survival extrapolations (they modify general population constraints on mortality rates and utilities). We have made the following edits to clarify this point: Page 13: "*Whilst the SACT data inform an economic scenario analysis, this only reflects the impact of SACT cohort demographics (age and gender) on general population mortality rates and utilities*" Page 19: "*The company explored the impact of the SACT population characteristics (age and gender) as a scenario analysis in their economic model*"

Issue 2 Scenario analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report comments on the scenario analyses presented and provides additional scenarios. Given the submission was for an abbreviated CDF review, Sanofi prioritised which scenarios were most relevant. This is in line with the CDF submission template which specifies that only the 5 most relevant scenarios are presented. Page 55: "*We consider that the company scenario analysis was limited.*"	Please acknowledge the limited number of scenarios that can be submitted within the CDF format. Please remove the statement: "We consider that the company scenario analysis was limited" as the Company were limited by the template guidance.	Currently the document may suggest the Company were unwilling to explore potentially relevant scenario analyses.	Not a factual inaccuracy. In their submission, the company do not provide: i) justification for the choice of scenarios; and ii) discussion of whether their scenarios are likely to have the most substantial impact that they consider plausible (as requested in the NICE CDF review template). For clarity, we have revised the text on page 55 as follows: *'We consider that the company have provided limited justification: (i) for their choice of scenario analyses and (ii) that other plausible scenarios would not have a more substantial impact on the cost-effectiveness results'*
The rationale for one of the scenarios noted on Page 7 is not quite clear. Page 7: "*For the comparison with best supportive care, the ICER ranged*	Please provide further rationale for why it is relevant to explore a scenario including patients at 81 years old rather than using the SACT baseline characteristics. Although stated in Table 14,	Statements may mislead the reader that the values are from the SACT dataset and are reflective of a UK cohort.	We agree that it is helpful to provide context for this scenario analysis and have added a reference to Strippoli et al. on page 7 and page 62.

between £32,646 (mean age at baseline of 81 years, 80% male) and £28,859 (no population adjustment of indirect comparison)." Page 62: "*(Scenario: Patient demographic with mean age of 81 years and 80% male)*"	clarification is required that these inputs are from the Italian study by Strippoli et al. on Page 7 and Page 62.		

Issue 3 End of life criteria versus chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14: "*However, their base case model indicates that the criteria are met for the comparison with BSC, but not for the comparison with chemotherapy (as the life expectancy exceeds 2 years). The ERG preferred scenario reiterates this conclusion.*" Although base case modelled survival for chemotherapy exceeds 24 months, this estimate should not be used in isolation to conclude that cemiplimab does not meet the end-of-life criteria when compared to chemotherapy. This estimate needs to be considered alongside all other available data on the survival of patients receiving chemotherapy and should include expert opinion.	Proposed amendment: Page 14: "However, their base case model indicates that the criteria are met for the comparison with BSC, but not for the comparison with chemotherapy (as the life expectancy exceeds 2 years. The ERG preferred scenario reiterates this conclusion. It should however be noted that both the company and ERG clinical experts suggested that survival would not be expected to exceed 2 years."	Although we acknowledge that the ERG concludes that whether cemiplimab meets the end-of-life criteria is uncertain, the report should put the base case modelled survival for chemotherapy in the context of clinical opinion and other available data. The company submission acknowledges that based on clinical expert opinion (which is in line with the ERG's expert clinical opinion) the base case chemotherapy OS extrapolation overestimates survival. This means that ICER estimates may be considered conservative, but	Not a factual inaccuracy. Considering the company's arguments, we have added a statement clarifying our position on page 14: *Overall, it remains unclear if cemiplimab meets end-of-life criteria due to high uncertainty in the comparator data. This issue warrants further discussion with clinical experts.*

		this should not be used to preclude cemiplimab from being considered an end-of-life medicine.	

Issue 4 Criticism of trial generalisability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 6: The SACT dataset has helped to establish that the company cemiplimab trials lack generalisability to UK clinical practice. Given the limitations of the SACT data as a RWD source and that data may have been influenced by the COVID-19 pandemic it isn't appropriate to reach such a strong conclusion.	Please remove this statement or acknowledge that it is not clear whether this is due to trials not being generalisable to the UK or that it is due to SACT being a RWD source. The differences between patients in real world studies and clinical trials is well established.	It may be incorrect to suggest that the trial is not generalisable to the UK based on the SACT data alone given its limitations. There is insufficient detail to understand the differences in actual clinical practice versus what happened in the trial to reach such a strong conclusion. On page 4 of the report the ERG state the following 'However, relatively limited population characteristics are reported for the SACT dataset, and generalisability of the findings may be influenced by the COVID-19 pandemic'	We have reduced the implied certainty of this inference by replacing "helped to establish" with "suggests".

Issue 5 Model data sources reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The report has the below statement, however, only Jarkowski was used as a source of PFS data. Page 65: The Company therefore relies on different sources to model OS and PFS for the chemotherapy comparator.	Page 65: The company uses the chart review to model OS and the Jarkowski study is the source of PFS data within the model for the chemotherapy comparator.	The original statement could be misinterpreted to read that multiple sources were used to inform one outcome.	Thank you for highlighting this. We have revised the text on page 65 as follows: *'The company therefore rely on different sources to model the survival parameters for the chemotherapy comparator: the chart review for OS and the Jarkowski study for PFS'*

Issue 6 Discrepancies in ICER results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54 "We found very small (£1) discrepancies with the reported incremental costs in the company's revised base case analyses that we could not explain, see Table 9 below for the ERG results."	The Company propose removal of the statement.	Please be advised ICERs presented in the Company submission were rounded to the nearest pound. This variation is likely due to the rounding of the ICERs	Not a factual inaccuracy. While the differences in results obtained by the ERG and the company are insignificant, we note that rounding of the ICERs does not explain them, as we also rounded the ICERs to the nearest pound. We have therefore made no change to this text.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 16: "*from [redacted]) with a maximum follow-up of [redacted]months*"	Data should be marked AIC	from [redacted] months) with a maximum follow-up of [redacted] months	We have updated the confidentiality marking on pages 16, 19 and 22 as suggested
Page 16: "*median follow up of [redacted] months (CS section A.6.1.2).*"	Data should be marked AIC	median follow up of [redacted] months (CS section A.6.1.2).	
Page 22: "*Site participation in the audit (which occurred during the COVID-19 pandemic) was voluntary. Of the original population, 52/106 patients from 12/25 of the centres were audited. The company integrated the data from these 52 audited patients into the original data set (i.e. N=106)*"	Data should be marked AIC	Site participation in the audit (which occurred during the COVID-19 pandemic) was voluntary. Of the original population, [redacted]106 patients from [redacted]/25 of the centres were audited. The company integrated the data from these [redacted]audited patients into the original data set (i.e. N=106)	
Page 37: "*The full ATC model has the advantage that it incorporates eight covariates whereas ATC model 1 incorporates seven. We note that the full ATC model incorporates one more covariate than the company's preferred ATT model 1 model and the histograms of weights are suggestive*	The full ATC model has the advantage that it incorporates eight covariates whereas ATC model 1 incorporates seven. We note that the full ATC model incorporates one more covariate than the company's preferred ATT model 1 model and the histograms of weights are		We have replaced "cf" with "compare"

of a marginally better balance for the full ATC model than ATT model 1 (cf Chart Review Figures 1-2 versus D1-D2)."	suggestive of a marginally better balance for the full ATC model than ATT model 1 (cf Chart Review Figures 1-2 versus D1-D2). Unclear of what this is supposed to be, possibly "compared with"?		
Page 51: "*Updated for 2018-2020 National Life Tables, England and Wales (ONS).20*"	Please correct referencing style		We have changed the reference citation number to a superscript, consistent with the referencing style elsewhere in the report.

Minor typos corrected by the ERG: We have changed "company does" to "company do" on pages 48 and 65, and "company reports" to "company report" on page 54. This is to address a minor inconsistency in reporting style.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592) [ID3883]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 22 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table N1 About you

Your name	Rohit Mistry
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Sanofi
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table N2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Generalisability of the clinical trial evidence for cemiplimab to UK practice (Report sections 3.1.2 and 3.1.3)	Yes	**Weight based and flat cemiplimab doses result in similar outcomes.** At the time of the requested data cut (July 2021), the number of patients within the group receiving 350mg every three weeks is 56. Aligned with previous data cuts, the data demonstrated comparability of safety and efficacy of the fixed and weight-based dose (Appendix A). **Cemiplimab is a step change in the treatment of locally advanced and metastatic CSCC patients in the UK.** Living with advanced (locally advanced and metastatic) CSCC is physically and emotionally challenging, and there is a high unmet need for new treatments. The introduction of cemiplimab as a treatment option for patients with advanced CSCC has resulted in a step change in the treatment pathway. Clinical experts consulted by both Sanofi and the ERG stated that they are now able to successfully treat a population that would otherwise be resigned to platinum-based chemotherapy or palliative care (BSC). The majority of advanced CSCC patients are not willing/able to tolerate chemotherapy, due to concerns about safety and the impact of these treatment options on their quality of life. However, Clinical experts

		have suggested that the safety and tolerability profile of cemiplimab means that more patients, including those who are older and frailer, are able and willing to initiate treatment. **Patients treated with cemiplimab in the UK are older than those enrolled in the cemiplimab clinical trials. However, the available SACT data is insufficient to reach a definitive conclusion on the generalisability of the cemiplimab trials to UK practice.** Of the 3 areas of clinical uncertainty identified in the managed access agreement, SACT data can only be used to reduce uncertainty around the baseline characteristics of patients to include in the economic model. Given that the SACT cohort reflects a patient population that is older than that enrolled in the cemiplimab trials and that clinicians have confirmed that they are comfortable treating older patients with cemiplimab, the Company have revised the economic base case to reflect the baseline characteristics of the SACT cohort. This is in line with the ERG's base case. However, given the limited information in terms of population characteristics reported for the SACT cohort, missing data, the potential impact of the SAR-CoV-2 pandemic (the pandemic), and the limited follow-up of the SACT dataset, it is difficult to draw firm conclusions on the basis of the SACT data alone as to whether the cemiplimab trials (Study 1423 and EMPOWER-CSCC 1) are generalisable to UK practice. The potential impact of the pandemic and the likely impact of key differences between the SACT cohort and the cemiplimab trials are discussed further below. • **Potential impact of COVID on the SACT cohort** Based on clinical expert feedback both the Company and the ERG have outlined possible ways in which the pandemic may have impacted the

		SACT data for cemiplimab. Clinical experts advising both the ERG and the Company reported that during the pandemic patients experienced delayed referrals and that patients were presenting to them with more advanced disease. As noted by Challapalli et al. in a recent publication relating to the UK Named Patient Programme (NPP) for cemiplimab, it is important to treat advanced CSCC patients quickly as progression of CSCC is often very rapid.(1) The authors note that they have seen more favourable results following increased awareness of cemiplimab and faster referral. Clinical experts also highlighted that there may have been extended dosing intervals and missed does of cemiplimab during the pandemic. It is therefore not possible to say whether the SACT data can be considered reflective of standard UK practice. • **Impact of age** As stated above the SACT cohort reflects a patient population that is older than that enrolled in the cemiplimab trials. However, we also note that the NPP cohort, identified by the ERG, reflects a slightly younger cohort of patients (74 [Challapalli et al. 2022 (1)] vs. 72 [cemiplimab trials] vs. 77 [SACT]). Data from the NPP were collected before the pandemic whereas the SACT data was predominately collected during the pandemic, which as previously mentioned may have impacted the treatment of advanced CSCC patients. Using baseline age from the SACT cohort in the economic model could therefore be considered a conservative assumption. The ERG report stated its "*clinical experts noted that cemiplimab may be less effective in older patients*." We are unaware of any evidence to suggest that age would impact the efficacy of cemiplimab, as demonstrated by Hober et al., 2021, a real-world evidence study on use of cemiplimab in France.(2) The study ran univariate and multivariate analyses and

		determined that age was not a prognostic factor associated with PFS (HR [univariate] = 1.00 [0.98-1.01] p= 0.62 and HR [multivariate] = 1.00 [0.98-1.01] p= 0.63) or OS (HR [univariate] = 1.00 [0.99-1.02] p= 0.81 and HR [multivariate] = 1.00 [0.98-1.01] p= 0.46). The Company do acknowledge that on average increasing age would limit a patient's ability to accrue the longer-term survival benefit associated with a treatment, due to the impact of general mortality on the risk of death. This is particularly relevant when considering the implications for economic evaluations, as the cost-effectiveness model assumes survival on cemiplimab cannot exceed age-related general mortality rates i.e., shows that patients are dying "with disease" not "from disease" due to the clinical effect of cemiplimab. This therefore limits the average accrual of benefits within the economic model over time. • **ECOG Performance status ≥2** The study design for EMPOWER-CSCC 1 and study 1423 excluded patients ECOG PS ≥2, as does the licence for cemiplimab. However, the Company and the ERG both note that the SACT dataset included potentially up to 18% (4% [n=14] reported and 14% [n=51] with missing data) of patients with ECOG PS ≥2. This is also the case for many of the other real world data sets for cemiplimab from other countries where patients with ECOG ≥2 (13.2-34% (1-9)), who were excluded from the trial, received cemiplimab in real-world settings-. These real word studies suggest that performance status impacts the efficacy of cemiplimab and should be considered a prognostic factor. For example, the French study from Hober et al. 2021 included 27% (n=66) ECOG PS ≥2 patients.(2) The univariate and multivariate analysis undertaken by Hober et al. 2021 suggests that ECOG PS ≥2 is a

		statistically significant prognostic factor associated with PFS and OS during the first 6 months. Where the highly significant impact of PS ≥ 2 on PFS (HR [univariate] = 2.3 [1.53 – 3.44] p= <0.0001 and HR [multivariate] = 2.33 [1.52-3.55] p= 0.0001) and OS (HR [univariate] = 4.39 [2.62-7.33] p=<0.0001 and HR [multivariate] = 4.56 [2.64-7.85] p= 0.0001) was confirmed during the first 6 months, after adjustment for age, sex, chronic dermatitis, primary CSCC site and disease stage.(2) This suggests that the inclusion of patients with ECOG PS ≥2 will result in poorer outcomes compared with the licenced population of ECOG PS ≤1 patients. Unfortunately, due to the limitations of the available SACT data (including limited information on population characteristics and missing data) and the fact that the data collection period coincided with the pandemic it is difficult to definitively conclude on the generalisability of the cemiplimab trials to UK practice. The Company therefore do not believe that it is appropriate to use the SACT dataset to validate the outcomes of the cemiplimab trials. Feedback from clinical experts, the named patient programme (1) and the Professional group submission to NICE from the British Association of Dermatologists (BAD) provided as part of the technical engagement papers for this appraisal all suggest that in practice clinicians are experiencing outcomes for their patients that are in line with their expectations based on the results of the cemiplimab trials.
Uncertainty in the clinical effectiveness of best supportive care and chemotherapy (Report section 3.1.5)	No	**Sanofi have invested in developing the comparative evidence base for CSCC. Whilst we acknowledge that there is remaining uncertainty, further analyses or data collection will not resolve this.** Generating evidence from real world data sources is often challenging. To ensure data reliability and data relevancy are achieved the study design should be appropriate, reproducible, but should also increase validity and

		reduce bias, a balance that is difficult to attain when access to data is limited.(10, 11) The Company have made a significant commitment and effort to strengthen the evidence base within advanced CSCC by conducting a retrospective chart review, undertaking reviews of the data, consulting clinical experts and conducting audits, to create a UK dataset that can be used to represent the population treated in the cemiplimab trials. Of the two comparators considered for this appraisal (platinum-based chemotherapy and BSC), the chart review was only able to provide significant new data for chemotherapy. As only a small number of eligible BSC patients were identified (n=[redacted]), these were excluded from the analysis informing the Company submission. Following discussion with clinical experts it is our understanding that this is likely to be attributed to the fact that patients treated with BSC are managed in primary care. The Company heard from its clinical experts that they rarely follow-up on patients once they have been referred to primary care for palliative care (BSC). Therefore, there is likely to be a large degree of selection bias for the BSC cohort identified in the chart review. For completeness the Company have provided updated OS data for the integrated cohort, including these [redacted]patients identified as BSC patients in response to technical engagement (Appendix B). [redacted] The ERG stated that they too did not identify any studies other than Sun et al. 2019 in the population of interest measuring the effect of BSC in their review.(12) Clinical experts interviewed as part of the Company's advisory board suggested that in the absence of any other data use of the Sun et al. 2019 publication was the most appropriate source of data to estimate the efficacy of BSC. The Company therefore maintain that in the absence of

		other data for BSC and given the challenges outlined above in terms of collecting data on BSC, the most appropriate evidence to utilise is from the Sun et al 2019 publication. This is further validated by additional clinical opinion sought by Sanofi to inform this technical engagement response. To inform this response Three clinicians were contacted for their views on the survival of patients receiving BSC. Estimates for median OS for these patients was 6 months, with no patients alive after 18 to 36 months. Outcomes reported by the retrospective chart review for platinum-based chemotherapy are aligned to those reported by Jarkowski et al. 2016 (13) which provides additional confidence in the results. However, clinical experts have consistently indicated that in their view both overestimate the survival benefits for patients receiving chemotherapy compared to what they have seen in practice. To inform this response Three clinicians were contacted for their views on the survival of patients receiving platinum-based chemotherapy. Estimates for median OS for these patients ranged from 9 to 12 months, with clinicians estimating 0%-10% of patients would be alive at 24 months. Although not without its own limitations, the Company maintain that the retrospective chart review is the best available evidence for chemotherapy and that using this data to inform indirect comparisons with cemiplimab will result in conservative estimates of comparative efficacy for cemiplimab. **Whilst the company acknowledge that there still remains a degree of uncertainty in the comparative evidence base (as would be expected in this disease area), we do not believe that further analyses or data collection will resolve this uncertainty. To account for the remaining uncertainty the Company have selected conservative assumptions to inform the Company base case with all plausible scenarios conducted by the Company and the ERG being significantly below the end of life**

		(EoL) WTP threshold. Although cemiplimab is being assessed under the old NICE methods we would also draw the committee's attention to the new NICE methods where a greater acceptance of uncertainty is advised in such circumstances.
Uncertainty in the clinical effectiveness of cemiplimab compared with best supportive care and chemotherapy (Report sections 3.1.6 and 3.1.7)	No	As acknowledged in the ERG report, Sanofi have followed best practice guidance for conducting ITCs in accordance with the NICE DSU TSD's. The remaining uncertainty results from the heterogeneity in the evidence base and the limited number of covariates reported by the included studies. As agreed with the ERG, alternative approaches/analyses are unlikely to have a significant impact on cost-effectiveness results.
Baseline characteristics of patients included in the model (Report section 4.2)	No	Clinical experts for both the Company and the ERG have suggested that to date patients treated with cemiplimab during its time in the CDF on average may be older that those seen in the cemiplimab clinical trials. Notwithstanding its limitations, this is supported by the SACT data. In acknowledgement of this, the Company have revised the economic base case to include the baseline characteristics from the SACT dataset, aligning with the ERGs preferred base case. We believe this to be a conservative assumption which is in line with the conservative approach we have taken throughout the analysis.
Uncertainty in the extrapolations of treatment effectiveness for cemiplimab, best supportive care and chemotherapy used in the model (Report sections 4.3 and 4.5)	Yes	As acknowledge in the ERGs report, the Company have followed guidance outlined in the NICE DSU TSD's on the extrapolation of survival. A summary of the OS parametric curve selection process and clarification on the rationale for curve section for cemiplimab, chemotherapy and BSC are presented in Appendix C. As demonstrated by the ERG, selection of alternative parametric distributions does not significantly impact the ICERs generated. Clinical experts have suggested the results can be considered an underestimation of the benefits associated with cemiplimab, given the

		conservative modelling assumptions (summarised in response to issue: End-of-life criteria) taken within the Company submission.
End-of-life criteria (Report section 7) The end-of-life criteria are: • The treatment is indicated for patients with a short life expectancy, normally less than 24 months • There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	No	**Cemiplimab is an end-of-life (EoL) treatment** The Company maintain that cemiplimab meets NICE's EoL criteria. Whilst the Company agree with the ERG that cemiplimab meets the EoL criteria versus BSC, the Company also strongly believe that the criteria should be considered met versus chemotherapy. The Company acknowledge that based on the chart review the modelled mean survival is above 24 months for chemotherapy, but highlight that this data is considered a significant overestimate of survival of patients treated with chemotherapy by clinicians and is heavily influenced by the tail of the curve (median survival = 15 months in both the Company chart review and the Jarkowski et al 2016 (13)). In preparation for technical engagement Sanofi contacted three clinicians to seek further views on the survival of advanced CSCC patients receiving either chemotherapy or BSC. A summary of clinical expert opinion are presented for chemotherapy and BSC in Figure 1 and Figure 2, respectively. **Figure 1: Clinical expert opinion on overall survival estimates for chemotherapy**

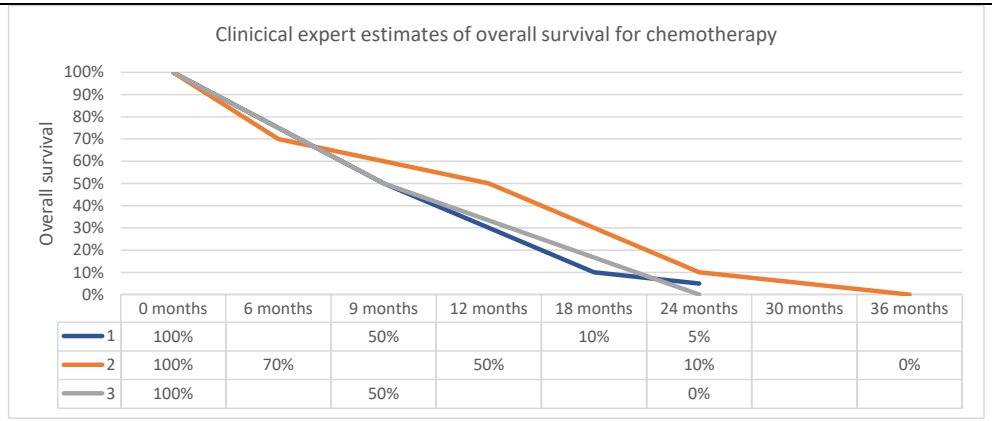
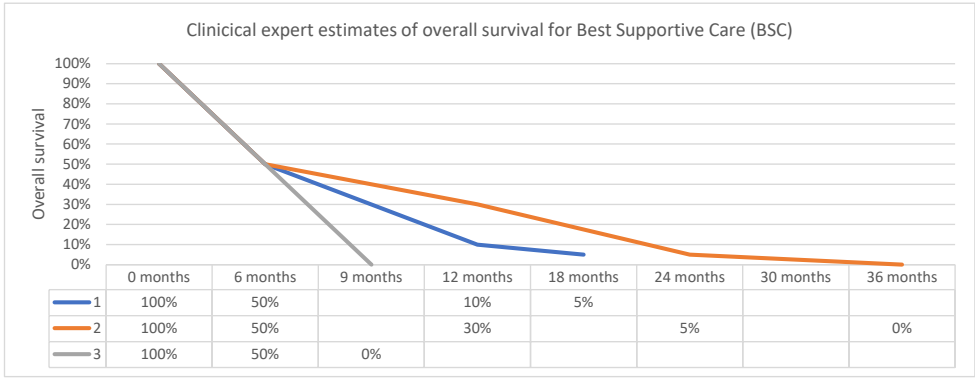


Figure 2: Clinical expert opinion on overall survival estimates for Best Supportive Care



Clinical experts indicated that they wouldn't expect any patients receiving chemotherapy to be alive after 2-3 years whereas the modelled chemotherapy curve doesn't hit zero within the 30-year life-time horizon modelled. Table 1 provides an analysis of restricted mean survival based on

the base case modelled survival curve for chemotherapy. Restricting survival to 3 years, in line with clinical opinion results in mean survival of less than 24 months.

Table 1: Restricted modelled mean survival on chemotherapy

Restriction	2 years	3 years	4 years	5 years
Chart review ATT, trimmed model 1 loglogistic extrapolation, life years undiscounted (life years discounted)	1.34 (1.30)	1.65 (1.59)	1.86 (1.77)	2.01 (1.90)
Jarkowski et al. (2016) (13) Gompertz extrapolation, life years undiscounted (life years discounted)	1.33 (1.29)	1.64 (1.58)	1.86 (1.77)	2.02 (1.91)

Given that only a relatively small proportion of patients who receive cemiplimab in the UK would be eligible for chemotherapy with the remainder receiving BSC, it is clear that cemiplimab meets the end-of-life criteria.

As discussed above, the Company have selected conservative base case assumptions in an acknowledgement of remaining uncertainty in the evidence base which are summarised in Table 2. This conservative approach should be taken into consideration by the committee in the context of their decision-making.

Table 2: Summary of key conservative assumptions

Conservative assumption	Impact on ICER
OS extrapolation for chemotherapy and BSC overestimates survival based on clinical opinion.	Clinical experts suggest that the available data which informs the base case overestimates survival for both

		BSC and chemotherapy. Underestimates benefit of cemiplimab. Overestimates ICER.
		Treatment duration for cemiplimab based on duration of PFS: Overestimates cemiplimab treatment cost thus overestimates ICER.
		No waning of treatment effect assumed after 5 years.: Underestimates cemiplimab benefit. Overestimates ICER. Assuming gradual waning between 5 and 8 years which is considered clinically plausible reduces the ICER.
		Baseline characteristics taken from SACT cohort: If a younger population is treated with cemiplimab post COVID, ICERs will be overestimated. Using age from the cemiplimab trials reduces the ICER.
		The availability of cemiplimab on the CDF has provided an underserved patient population with a novel, effective and tolerable treatment where previously there was no licenced, effective treatment available. It is therefore critical that patients continue to have access to cemiplimab and that cemiplimab is recommended for routine commissioning. Of the three areas of clinical uncertainty outlined in the managed access agreement for cemiplimab, two have been resolved by managed access: the baseline characteristics to include in the economic model and the long-term treatment benefit of cemiplimab (magnitude of continued treatment benefit after a stopping rule**).** Given challenges in collecting real world evidence, particularly for BSC in advanced CSCC, there is remaining uncertainty with respect to the comparator data for cemiplimab and therefore comparative effectiveness. However, we urge the committee to consider the remaining uncertainty in the context of the conservative

		assumptions used, the significant unmet need in this patient population and the dramatic difference that cemiplimab has made to patients whilst available on the CDF.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table N3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Differences between original chart review and audit	3.1.5.1 Company chart review: chemotherapy (OS)	Yes	Further details on the differences between the original chart review and audit are presented in Appendix D.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table N4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)		
			Analysis	vs. BSC	vs. Chemotherapy
Generalisability of the clinical trial evidence for cemiplimab to UK practice	Baseline characteristics used in the economic evaluation was aligned to the cemiplimab trials (Study 1423 and EMPOWER-CSCC 1)	Alignment to the ERGs preferred base case using the baseline characteristics aligned to the SACT dataset.	**Company's base case before technical engagement**	£29,438	£36,163
			Company's revised base case	£30,952.40	£37,774.61
Company's base case following technical engagement (or revised base case)					
	Incremental QALYs: [QQQ]	**Incremental costs: [£££]**		**Please provide company revised base-case ICER**	
BSC	[redacted]	[redacted]		£30,952.40	
Chemotherapy	[redacted]	[redacted]			£37,774.61

Table N5: Sensitivity analyses around revised base case

Scenario	BSC			Chemotherapy		
	Inc. QALYs	Inc. Cost	ICER	Inc. QALYs	Inc. Cost	ICER

Revised Company base case	[redacted]	[redacted]	£30,952	[redacted]	[redacted]	£37,775
1) Comparator survival: Jarkowski OS (Gompertz) and PFS (Weibull)	[redacted]	[redacted]	£42,179	[redacted]	[redacted]	£38,930
2) Population adjustment: ATC model 1				[redacted]	[redacted]	£41,021
3) Population adjustment: ATT full model				[redacted]	[redacted]	£38,531
4) SACT baseline characteristics: mean age 77 years, 74% male	**Revised company base case**					
5) No waning of treatment benefit	[redacted]	[redacted]	£26,738	[redacted]	[redacted]	£29,276
6) Waning between 60 and 96 months	[redacted]	[redacted]	£27,475	[redacted]	[redacted]	£33,942

Appendix A: Efficacy and Safety analyses from EMPOWER-CSCC 1 July 2021 data cut off

In addition to the responses provided as part of the response to Clarification Questions A2, A27, A28 we have included efficacy and safety analyses from EMPOWER-CSCC 1 using the July 2021 data cut by trial group.

A summary of the analyses provided are presented below:

- Table 3: Best Overall Tumor Response Rate by Independent Central Review (Full Analysis Set)
- Table 4: Kaplan-Meier Estimation of Duration of Response by Independent Central Review (Full Analysis Set - Patients with Confirmed CR or PR)
- Table 5: Observed Duration of Response by Independent Central Review (Full Analysis Set - Patients with Confirmed CR or PR)Table 5: Observed Duration of Response by Independent Central Review (Full Analysis Set - Patients with Confirmed CR or PR)
- Table 6: Best Overall Tumor Response Rate for Patients with Confirmed Pathology Review by Independent Central Review (Full Analysis Set - Patients with Confirmed Central Pathology Review)
- Table 7: Kaplan-Meier Estimation of PFS by Independent Central Review (Full Analysis Set)Table 7: Kaplan-Meier Estimation of PFS by Independent Central Review (Full Analysis Set)
- Table 8: Summary of Overall Survival (Full Analysis Set)
- Table 9: Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)
- Table 10: Summary of Common (>=5%) Treatment-Emergent Adverse Events by Preferred Term and NCI Grade (Safety Analysis Set))

Table 3: Best Overall Tumor Response Rate by Independent Central Review (Full Analysis Set)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)	mCSCC Cemiplimab: 350 mg Q3W (N=56)	Total (N=193)
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	[redacted]	[redacted]	[redacted]	[redacted]
Partial Response (PR) [a]	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease (SD) [b]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CR/Non-PD [c]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable (NE) [d]	[redacted]	[redacted]	[redacted]	[redacted]
Response				
Objective Response Rate (ORR: CR+PR)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for ORR [e]	[redacted]	[redacted]	[redacted]	[redacted]
Complete Response Rate (CR) [a]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for CR Rate [e]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for DCR [e]	[redacted]	[redacted]	[redacted]	[redacted]
Durable DCR [f]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for Durable DCR [e]	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off as of Jul 1st, 2021. (Table 14.2.1.1f)

[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.

[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date.

[c] Non-CR/Non-PD is for patients with non-measurable disease only.

[d] Not evaluable response includes the missing and unknown tumor response.

[e] Clopper-Person exact confidence interval.

[f] Durable DCR: proportion of patients with CR, PR, SD or non-CR/Non-PD for at least 105 days without PD.

Table 4: Kaplan-Meier Estimation of Duration of Response by Independent Central Review (Full Analysis Set - Patients with Confirmed CR or PR)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=[redacted])	laCSCC Cemiplimab: 3 mg/kg Q2W (N=[redacted])	mCSCC Cemiplimab: 350 mg Q3W (N=[redacted])	Total (N=[redacted])
KM Estimation of Duration of Response (CR or PR)				
N				
Number of events, n (%) [a]				
Number of censored patients, n (%) [a]				
Median (95% CI), (months)				
Estimated Event-Free Probability, % (95% CI)				
4 months				
6 months				
8 months				
12 months				
16 months				
20 months				
24 months				
28 months				
32 months				
36 months				
40 months				
[redacted]				

[a] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.

Table 5: Observed Duration of Response by Independent Central Review (Full Analysis Set - Patients with Confirmed CR or PR)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=[redacted])	laCSCC Cemiplimab: 3 mg/kg Q2W (N=[redacted])	mCSCC Cemiplimab: 350 mg Q3W (N=[redacted])	Total (N=[redacted])
Observed Duration of Response (CR or PR) (months)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Min : Max	[redacted]	[redacted]	[redacted]	[redacted]
Observed Duration of Response (CR or PR), n (%) [a]				
>=4 months	[redacted]	[redacted]	[redacted]	[redacted]
>=6 months	[redacted]	[redacted]	[redacted]	[redacted]
>=8 months	[redacted]	[redacted]	[redacted]	[redacted]
>=12 months	[redacted]	[redacted]	[redacted]	[redacted]
>= 16 months	[redacted]	[redacted]	[redacted]	[redacted]
>= 20 months	[redacted]	[redacted]	[redacted]	[redacted]
>= 24 months	[redacted]	[redacted]	[redacted]	[redacted]
>= 28 months	[redacted]	[redacted]	[redacted]	[redacted]
>= 32 months	[redacted]	[redacted]	[redacted]	[redacted]
>= 36 months	[redacted]	[redacted]	[redacted]	[redacted]
>= 40 months	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off as of Jul 1st,¬ 2021. (Table 14.2.1.5f)

[a] Percentages are based on number of patients with confirmed CR or PR. The numerator includes the number of patients whose observed duration of response reached at least the specified time. Patients who did not have the opportunity to reach the specified timepoint were included in the denominator only. Because responses for some patients are ongoing, the percentages at the specified timepoints may increase as data mature.

Table 6: Best Overall Tumor Response Rate for Patients with Confirmed Pathology Review by Independent Central Review (Full Analysis Set - Patients with Confirmed Central Pathology Review)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=[redacted])	laCSCC Cemiplimab: 3 mg/kg Q2W (N=[redacted])	mCSCC Cemiplimab: 350 mg Q3W (N=[redacted])	Total (N=[redacted])
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	[redacted]	[redacted]	[redacted]	[redacted]
Partial Response (PR) [a]	[redacted]	[redacted]	[redacted]	[redacted]
Stable Disease (SD) [b]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CR/Non-PD [c]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable (NE) [d]	[redacted]	[redacted]	[redacted]	[redacted]
Response				
Objective Response Rate (ORR: CR+PR)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for ORR [e]	[redacted]	[redacted]	[redacted]	[redacted]
Complete Response Rate (CR) [a]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for CR Rate [e]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for DCR [e]	[redacted]	[redacted]	[redacted]	[redacted]
Durable DCR [f]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for Durable DCR [e]	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off as of Jul 1st, 2021. (Table 14.2.1.9f)
[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date.
[c] Non-CR/Non-PD is for patients with non-measurable disease only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Person exact confidence interval.
[f] Durable DCR: proportion of patients with CR, PR, SD or Non-CR/Non-PD for at least 105 days without PD.

Table 7: Kaplan-Meier Estimation of PFS by Independent Central Review (Full Analysis Set)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)	mCSCC Cemiplimab: 350 mg Q3W (N=56)	Total (N=193)
KM estimation of Progression Free Survival				
Number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of censored patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI), (months)	[redacted]	[redacted]	[redacted]	[redacted]
Estimated Event-Free Probability, % (95% CI)				
4 months	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
8 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
16 months	[redacted]	[redacted]	[redacted]	[redacted]
20 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
28 months	[redacted]	[redacted]	[redacted]	[redacted]
32 months	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
40 months	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off as of Jul 1st, 2021. (Table 14.2.2.1f)

Table 8: Summary of Overall Survival (Full Analysis Set)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)	mCSCC Cemiplimab: 350 mg Q3W (N=56)	Total (N=193)
KM estimation of Overall Survival				
Number of deaths, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of censored patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI), (months)	[redacted]	[redacted]	[redacted]	[redacted]
Estimated Probability of Survival, % (95% CI)				
4 months	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
8 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
16 months	[redacted]	[redacted]	[redacted]	[redacted]
20 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
28 months	[redacted]	[redacted]	[redacted]	[redacted]
32 months	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
40 months	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off as of Jul 1st, 2021. (Table 14.2.3.1f)

Table 9: Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)	mCSCC Cemiplimab: 350 mg Q3W (N=56)	Total (N=193)
Number ofTEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Number of NCI grade 3/4/5TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Number of seriousTEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with anyTEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with any NCI grade 3/4/5TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with any seriousTEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients who discontinued study treatment due toTEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with anyTEAE leading to a drug interruption/delay, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with anyTEAE leading to a dose reduction, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with anyTEAE leading to both a drug interruption/delay and a dose reduction, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with anyTEAE resulting in death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off as of Jul 1st, 2021. (Table 14.3.1.2.1)
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 10: Summary of Common (>=5%) Treatment-Emergent Adverse Events by Preferred Term and NCI Grade (Safety Analysis Set))

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)		laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)		mCSCC Cemiplimab: 350 mg Q3W (N=56)		Total (N=193)	
Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Patients with any TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actinic keratosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred Term, n (%)	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)		laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)		mCSCC Cemiplimab: 350 mg Q3W (N=56)		Total (N=193)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Fall	[redacted]							
Urinary tract infection								
Wound infection								
Blood creatinine increased								
Hypertension								
Oedema peripheral								
Pain in extremity								
Pneumonitis								
Cellulitis								
Hypokalaemia								
Insomnia								
Aspartate aminotransferase increased								
Skin infection								
Blood alkaline phosphatase increased								
Myalgia								
Dry mouth								
Hyperuricaemia								
Nasopharyngitis								
Oropharyngeal pain								
Pneumonia								
Pyrexia								
Squamous cell carcinoma of skin								
Weight decreased								
Chills								
Dysphagia								
Hypomagnesaemia								
Nasal congestion								
Dehydration								
Depression								
Hyperglycaemia								
Hyperkalaemia								

Preferred Term, n (%)	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)		laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)		mCSCC Cemiplimab: 350 mg Q3W (N=56)		Total (N=193)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Hypotension	[redacted]							
Infusion related reaction	[redacted]							
Neck pain	[redacted]							
Atrial fibrillation	[redacted]							
Bronchitis	[redacted]							
Epistaxis	[redacted]							
Gastrooesophageal reflux disease	[redacted]							
Lacrimation increased	[redacted]							
Oral candidiasis	[redacted]							
Paraesthesia	[redacted]							
Delirium	[redacted]							
Dysgeusia	[redacted]							
Hypercalcaemia	[redacted]							
Hyponatraemia	[redacted]							
Skin laceration	[redacted]							
Squamous cell carcinoma	[redacted]							
Contusion	[redacted]							
Eye swelling	[redacted]							
Facial pain	[redacted]							
Haematuria	[redacted]							
Lymphocyte count decreased	[redacted]							
Lymphoedema	[redacted]							
Memory impairment	[redacted]							
Muscular weakness	[redacted]							
Skin lesion	[redacted]							
Thrombocytopenia	[redacted]							
Toothache	[redacted]							
Tumour pain	[redacted]							
Dry eye	[redacted]							
Dysphonia	[redacted]							
Hypoglycaemia	[redacted]							

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)		laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)		mCSCC Cemiplimab: 350 mg Q3W (N=56)		Total (N=193)	
Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off as of Jul 1st, 2021. (Table 14.3.1.4.6)
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1. NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a preferred term.
The table is sorted by decreasing frequency of all grades in the total group.

Appendix B: Including BSC patients (n=4) in integrated cohort

Figure 3: KM OS curves from the chart review including four patients with ECOG 0-1 at advanced diagnosis (index for OS measured from advanced diagnosis, rather than from initiation of first-line therapy)

Appendix C: Parametric curve selection

Curve selection approach

Model fit was evaluated using the following technical and clinical validation criteria:

Technical validation criteria

- Goodness of fit: The fit of the competing statistical models to the data were compared with the Akaike information criterion (AIC), Bayesian information criterion (BIC) and using visual inspection.

- Compatibility of models for the reference curve and hazard ratios: The compatibility of each reference distribution with the best fitting models was considered. The models included are commonly used for survival extrapolation for cost-effectiveness analysis and were included in order to validate the outcomes estimated.

Clinical validation criteria

- The tails of the modelled PFS and OS functions were inspected to assess the clinical plausibility of the extrapolation of PFS and OS beyond trial follow-up.

- External validation data for cemiplimab, chemotherapy and BSC OS: Extrapolations were clinically validated based on landmark analysis estimates elicited from clinical experts during an HTA advisory board in December 2021.

- Relationship between PFS and OS: The model includes a check to ensure that the PFS and OS curves cannot cross, but this was also included as a clinical validation step at model selection stage, as crossing of the uncontrolled curves could undermine confidence in the extrapolations. The estimated post-progression survival was also reviewed at model selection stage, as extrapolations which estimate a higher level of post-progression survival benefit may lead to higher uncertainty in the cost-effectiveness results.

- General mortality: An adjustment was made to ensure that the mortality estimated by the OS curves could not drop below the age-specific level of mortality estimated in the general UK population.

Overall Survival - Cemiplimab (Lognormal)

Table 11 presents a summary of considerations for the curve selection for cemiplimab.

The best fitting curves based on statistical fit for the overall survival of cemiplimab are the P(0,-1) (AIC = 823.16, BIC = 833.32) and Lognormal (AIC = 823.28, BIC 830.05).

Clinical experts consulted as part of the Company advisory board (December 2021) suggested the p(0,-1), p(0,-0.5), p(1,0), p(1,0.5) and lognormal curves would align with their estimates of cemiplimab survival.

On review of clinical expert opinion and statistical fit, the lognormal distribution was selected as the Company base case, this also align with the assumptions used as in TA592.

Table 11: Overall survival for cemiplimab (pooled EMPOWER-CSCC 1 and Study 1423), goodness of fit (CEA TR)

Model	Goodness of fit to data (up to 60 months)			Clinical and epidemiological plausibility of extrapolation (>60 months)		
	AIC	BIC	Goodness of fit	OS at 120 months	Extrapolation	Plausibility based on visual inspection
Weibull (P1=0)	828.34	835.12	×	34%	Decreases over time	✓
Second-order FP P1=0, P2=-1	823.16	833.32	✓	43%	Decreases over time	✓
Second-order FP P1=0, P2=-0.5	824.06	834.23	✓	44%	Decreases over time	✓
Second-order FP P1=0, P2=0	923.11	933.28	×	61%	Plateaus	×
Second-order FP P1=0, P2=0.5	826.75	836.92	×	48%	Plateaus	×
Second-order FP P1=0, P2=1	827.96	838.12	×	50%	Plateaus	×
P1=1 (Gompertz)	825.98	832.75	✓	50%	Plateaus	×
Second-order FP P1=1, P2=-1	826.76	836.92	×	52%	Plateaus	×
Second-order FP P1=1, P2=-0.5	827.59	837.76	×	52%	Plateaus	×
Second-order FP P1=1, P2=0	827.96	838.12	×	50%	Plateaus	×
Second-order FP P1=1, P2=0.5	827.42	837.59	×	44%	Decreases over time	✓
Second-order FP P1=1, P2=1	826.80	836.97	×	31%	Decreases over time	✓
Log-normal	823.28	830.05	✓	42%	Decreases over time	✓
Log-logistic	826.50	833.28	×	40%	Decreases over time	✓

Notes: X indicates more than three points difference from the lowest AIC/BIC. Abbreviations: Akaike Information Criterion; AIC; Bayesian Information Criterion; BIC; FP, fractional polynomial; OS, overall survival.

Overall Survival - Chemotherapy (log-logistic)

Table 12 presents a summary of considerations for the curve selection for cemiplimab.

Based on statistical fit the second-order fractional polynomials, p= (1, 0.5) and p = (1, -0.5) offer the best statistical fit.

However, clinical expert opinion during the Company advisory board (December 2021) suggested that the survival associated with these extrapolations is an overestimation of the long term survival. Clinicians who stated they would have expected the curve to cross zero at a much earlier time point (i.e., within 3 to 5 years). Unlike for cemiplimab (and other immunotherapies) you would not expect the survival cure to plateau. For this reason, any curves with a plateau were excluded.

The log-logistic extrapolation was selected in the Company base case, as the curve provided a survival estimate for chemotherapy that were not overly optimistic. Arguably a log normal or Weibull curve could also have been selected.

The ERG report includes scenarios using alternative extrapolations, as noted these have a limited impact on the ICER.

Table 12: Overall survival for ATT adjusted (model 1) chart review (integrated UK analysis cohort, n=[redacted]), goodness of fit (CEA TR)

Model	Goodness of fit to data (up to 16 months)			Clinical and epidemiological plausibility of extrapolation [redacted] months)		
	AIC	BIC	Goodness of fit	OS at 120 months	Extrapolation	Plausibility based on visual inspection
Weibull (P1=0)	1020.21	1024.40	×	1%	Decreases over time	✓
Second-order FP P1=0, P2=-1	995.11	1001.40	×	9%	Decreases over time	✓
Second-order FP P1=0, P2=-0.5	990.56	996.84	×	13%	Decreases over time	✓
Second-order FP P1=0, P2=0	987.53	993.81	✓	16%	Plateaus	×
Second-order FP P1=0, P2=0.5	986.49	992.77	✓	19%	Plateaus	×
Second-order FP P1=0, P2=1	988.09	994.38	✓	20%	Plateaus	×
P1=1 (Gompertz)	1014.53	1018.72	×	10%	Decreases over time	✓
Second-order FP P1=1, P2=-1	989.01	995.29	✓	18%	Plateaus	×
Second-order FP P1=1, P2=-0.5	987.30	993.58	✓	19%	Plateaus	×
Second-order FP P1=1, P2=0	988.09	994.38	✓	20%	Plateaus	×
Second-order FP P1=1, P2=0.5	991.81	998.09	×	21%	Plateaus	×
Second-order FP P1=1, P2=1	996.91	1003.19	×	20%	Plateaus	×
Log-normal	995.32	999.51	×	5%	Decreases over time	✓
Log-logistic	996.30	1000.49	×	5%	Decreases over time	✓

Notes: X indicates more than three points difference from the lowest AIC/BIC. Abbreviations: Akaike Information Criterion; AIC; Bayesian Information Criterion; BIC; FP, fractional polynomial; OS, overall survival.

Overall Survival - BSC; (log-logistic)

Table 13 presents a summary of the statistical fit goodness of fit for OS of BSC using Sun et al. 2019. The best statistical fit (AIC and BIC) models include the p(0,-1), p(0,-0.5), lognormal and log-logistic extrapolations.

As can be seen upon visual inspection of the BSC extrapolations (Figure 4), the curves are very similar, with little difference in the tail of the curve extrapolations.

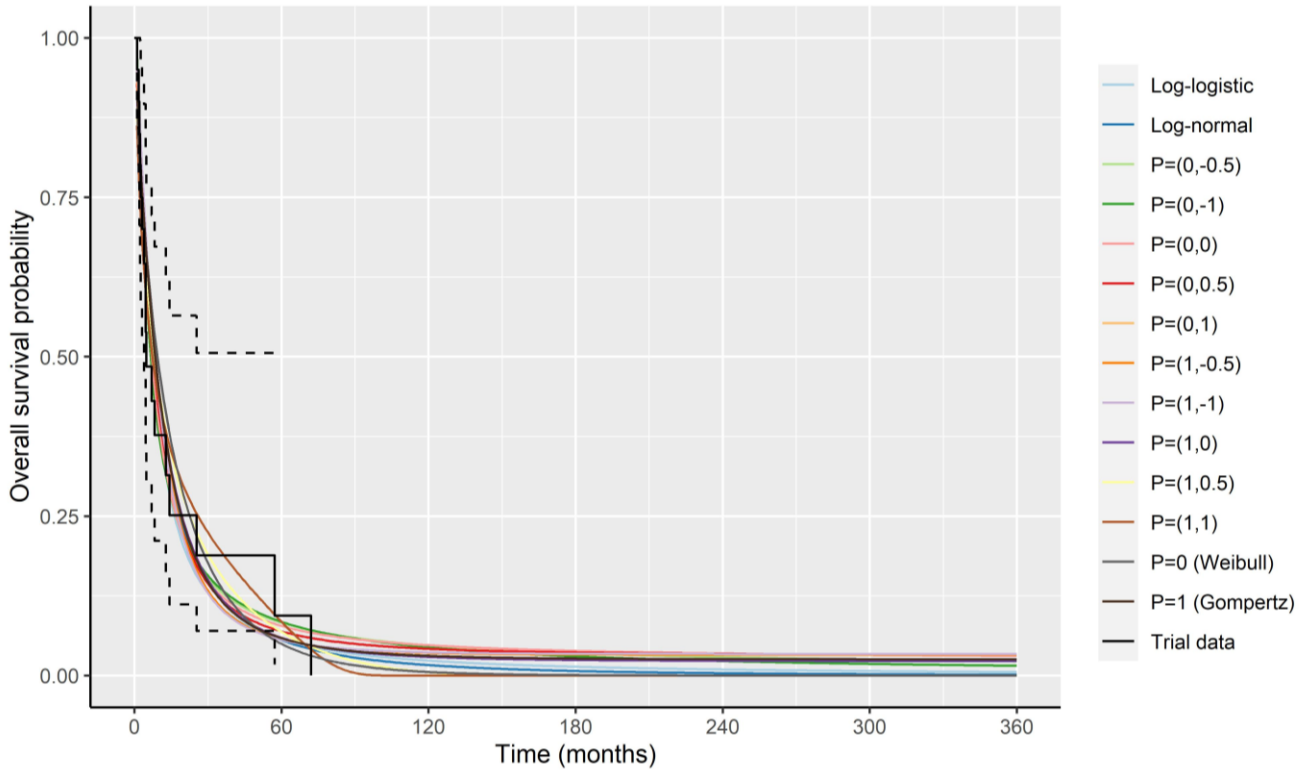
The log-logistic extrapolation was chosen as the Company base case curve for BSC, as this curve runs through the middle of the extrapolated curves and has a decreasing extrapolation over time. However, this may also be deemed an overestimation based on the comments made by clinicians with respect to the chemotherapy extrapolations (i.e., they would expect to see the curve cross zero by 3 to 5 years).

Table 13: Naïve Overall survival for best supportive care using Sun et al. 2019 goodness of fit (CEA TR)

Model	AIC	BIC
Weibull (p0)	131.57	133.56
Second-order FP (p0 p-1)	127.09	130.08
Second-order FP (p0 p-0.5)	128.04	131.03
Second-order FP (p0 p0)	129.53	132.51
Second-order FP (p0 p0.5)	131.34	134.33
Second-order FP (p0 p1)	132.79	135.78
Gompertz (p1)	130.81	132.80
Second-order FP (p1 p-1)	131.59	134.58
Second-order FP (p1 p-0.5)	132.36	135.34
Second-order FP (p1 p0)	132.79	135.78
Second-order FP (p1 p0.5)	131.69	134.68
Second-order FP (p1 p1)	129.76	132.74
Lognormal	127.21	129.21
Loglogistic	128.12	130.12

AIC, Akaike information criterion; BIC, Bayesian information criterion; FP, Fractional polynomial

Figure 4: Extrapolated overall survival for best supportive care estimated using alternative parametric models based on naïve analysis (Sun et al. 2019)



As with chemotherapy, the selection of alternative distributions for BSC did not have a significant impact on ICERs (see ERGs table of additional scenarios).

Appendix D: Chart review: differences between the original and audit datasets

- CRFs: Confirmation that the investigators expected to complete all fields
    - The protocol for the study included checks for data quality control, to minimize missing or incomplete data. Data validation, resubmission of data for key data points such as date of diagnosis, date of therapy initiation, hospitalizations, patient status (alive or deceased) of at least 30% of completed CRFs were conducted. Range checks, CRF scanning for data inconsistency, data entry, reporting of the proportion of missing data at the item and individual level, examination of frequencies and distributions, as well as the generation of descriptive statistics, was conducted for 30% of the completed CRFs to be implemented online. Internet-based CRF also promoted data completeness by not allowing physicians to advance to subsequent sections until required fields were entered.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Guidance review following a period of managed access

Clinical expert statement

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592) [ID3883]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Andrew Sykes**
2. Name of organisation	**Christie Hospital NHS Foundation Trust**

NICE National Institute for Health and Care Excellence

3. Job title or position	**Consultant Clinical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. Do you have a conflict of interest that you wish to declare[1]?	Direct /Indirect – please explain Yes - honoraria for lecturing on Cemiplimab paid by SANFI (£420 Jan 2022)

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

7. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
8. What is the main aim of treatment?	For cancer drugs please delete as appropriate: palliative Other, please describe
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A combined partial/complete response rate of 20% or more, or an improvement in survival of greater than 3 months
10. What are the benefits that you expect the technology to	Health benefits. Please delete as appropriate: Increased survival Y Increased time to progression Y

provide compared with routinely commissioned care?	Improved QOL Y Does the new technology provide other substantial health related benefits not included in the QALY calculation? N, please explain: Non-health benefits. Please delete as appropriate: Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y/N, please explain: Improved accessibility to patients Y/N, please explain: Implications for delivery of the NHS service Y/N, please explain:
11. Are there any recognised side effects of the technology?	If yes, please explain how they may affect the patient's quality of life Yes, as with all immunotherapy there are non-immune related and immune related toxicities. On the whole though these toxicities are very manageable and fewer than conventional chemotherapy. They are significantly outweighed for a large proportion of patients by the benefit of tumour control. In my experience Cemiplimab improves patient quality of life as well as extending it.

12.Are there any important outcome data that were not collected during the managed access period?	Not that I am aware of
13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	Prior to the use of cemiplimab there was very little or no treatment for advanced, metastatic cutaneous SCC. Very few patients would be eligible for chemotherapy and even when they were, responses were rare and very short lived. In my own practice I might use chemotherapy on less than one patient per year. This compares with cemiplimab which I will start on approximately 20 new patients annually. Cemiplimab has completely changed the treatment paradigm for these patients
14. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, as above I think that cemiplimab has changed the treatment paradigm for cSCC. We now have a treatment that provides effective tumour control for a significant proportion of our patients with minimal toxicity. Previously the best we could offer most of our patients was best supportive care. In practice this meant discharging patients to the care of their GP/hospice for terminal care. There is an almost complete lack of data on survival of patients with advance, metastatic sSCC. There are a number of reasons for this, but partly it is because the lack of treatment options meant that these patients were not followed up in the hospital setting and so accurate data is not there to collect. Cemiplimab now gives us a well-tolerated, effective treatment that improves survival and quality of life for these patients.
15. Are there any groups of patients who might	Patients with solid organ transplants and immune related conditions are harder to manage because of the mode of action of immunotherapy, but even they can benefit and should not automatically be denied access to the drug. In practice they seem to be just as likely to respond to treatment.

benefit more or less from the technology than others?	
What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	We currently have access to cemiplimab through the cancer drug fund/bluteq application process. The bluteq application process stipulates the conditions under which we can prescribe cemiplimab. There are a number guidelines for the treatment of immune related toxicity such as the ESMO/NCCN guidelines
17. Are there other clinical pathways used in England other than those recommended in the guideline?	N
18. Would the new technology require a change in the clinical pathway?	N
19. Will the technology introduce new costs to the	There are minor costs around the delivery of immunotherapy, but otherwise no.

NHS or patients other than for the technology itself?	
20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	There are stopping rules as part of the CDF/bluteq application. Treatment can continue for up to 2 year in the absence of unmanageable toxicity or disease progression.
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: As discussed earlier Cemiplimab has changed the treatment paradigm. We now have a well-tolerated effective treatment for the management of advanced, metastatic cSCC I have used the treatment for over 2 years and have seen numerous responses, both complete and partial. I have patients who remain alive and well more than 2 years after starting treatment. Negative: have no negatives

22. Did any people decline treatment? What were their reasons why?	No, not in my practice
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	The process has been very straightforward. We already have a large practice of patients receiving immunotherapy for head and neck cancer and we have included our cSCC patients in that clinic. In my experience cSCC patients are easier to treat because they have a higher response rate and survival and toxicity is no worse, despite the average age of cSCC patients being a decade older.
24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How?	Prior to the availability of cemiplimab there was no available treatment for the majority of these patients and they were referred back to general practice/hospices for terminal care. The introduction of cemiplimab has clearly changed our practice. We now have 30+ patients actively on treatment or follow up after 2 years of treatment.
25. Are there other points of learning arising from the period of the managed access	No

agreement that you would like considered?	
Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	NO
Equality	
31a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

Key issues for engagement

All: Please use the table below if you would like to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Generalisability of the clinical trial evidence for cemiplimab to UK practice (Report sections 3.1.2 and 3.1.3) *Are the characteristics and outcomes of people included in the SACT dataset generalisable to UK practice?*	Yes	I believe that the SACT data is likely to be representative of UK practice. The SACT data may not be comparable with trial data though for a number of reasons 1. Trial patients are generally a selected group who are younger and fitter and therefore tend to have better survival regardless of treatment 2. The SACT data was compiled during a time of disruption due to COVID which is likely to have worsened outcome for a variety of reasons including delayed treatment. 3. The SACT data was include patients treated in the learning curve of immunotherapy. This is always more significant for the general population when patients are treated in smaller centres with less experience. This was noticeable in the named patient scheme where from my own experience patients were selected for treatment at a later stage than we would now do. As a consequence they had more advanced disease and did worse than expected (i) i. Journal of the European Academy of Dermatology and Venereology Cemiplimab in advanced cutaneous squamous cell carcinoma: the UK experience from the Named Patient Scheme DOI: https://doi.org/10.1111/jdv.18082
Uncertainty in the clinical effectiveness of best supportive care and chemotherapy (Report section 3.1.5) *Are the characteristics and outcomes of people included in the company UK chart review aligned with your experience in UK practice?*	Yes	Unfortunately our evidence of the effectiveness of best supportive care is very poor. Possibly the best data comes from Cowey et al (1) who looked at patients treated with systemic chemotherapy and found a median survival rate of 15-16 months. Patients fit for chemotherapy are a highly selected group however and would expect to have a better survival than the general population of patient with cSCC. The 3 studies in the report (section 3.1.5) are all equally unreliable as measures of best supportive care. They are all highly selective of patients fit for chemotherapy because in

		general, when no treatment is available patients are not regularly seen in secondary/tertiary care and so chart review is extremely selective. My own clinical experience of managing patient with advanced/metastatic cSCC is that survival is less than 12 months. 1. Clinical outcomes among unresectable, locally advanced, and metastatic cutaneous squamous cell carcinoma patients treated with systemic therapy. Cowey CL, Robert NJ, Espirito JL, Davies K, Frytak J, Lowy I, Fury MG Cancer Med. 2020;9(20):7381. Epub 2020 Jun 24.
Uncertainty in the clinical effectiveness of cemiplimab compared with best supportive care and chemotherapy (Report sections 3.1.6 and 3.1.7)	Yes	The lack of historical data for best supportive care makes comparison with cemiplimab difficult. However previously I would treat less than one patient per year with systemic therapy and I now treat approximately 20 annually for cemiplimab. I currently have 30+ patients on ongoing treatment.
Baseline characteristics of patients included in the model (Report section 4.2) *Does the ERG's preferred assumption of using the demographics of the SACT cohort reflect your experience with patients in the NHS?*	Yes	My experience is more in keeping with that of the SACT database than the clinical trial. See below for an analysis of patients treated in my centre as of November 2021 **40 patients treated with cemiplimab in 2 years (4 compassionate use program and 36 CDF)** **Of the 32 patients treated on CDF:** **Median age 78 (45-86)** **Median age of responders is 6 years older than non-responders** **Median no of cycles cemiplimab 14 (1-35)** **3 patients have completed 2 years treatment, 18 remain on treatment, 11 patients stopped treatment with disease progression.** **Best response to cemiplimab:** **CR 10** **PR 9** **SD 6** **Crude disease control rate of 70% (72% in EMPOWER)**
Uncertainty in the extrapolations of treatment effectiveness for cemiplimab, best supportive care and chemotherapy used in the model (Report sections 4.3 and 4.5) *Would you expect patients in the NHS to do less well in terms of OS and PFS compared with the clinical trial data?*	No	It is recognised that patients in clinical trials are almost always younger and fitter than those of the general population and so would be expected to have better survival. This is reflected in the SACT data and my own experience as above. Despite this my experience with cemiplimab is broadly in line with the clinical trial data despite the population differencese.

End of life criteria (Report section 7) *What is the life expectancy of patients receiving best supportive care or chemotherapy for advanced CSCC in the UK?*	Yes/No	There is no data for this in the UK, but my experience is that survival is less than 12 months.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592) [ID3883]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 22 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	[redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Generalisability of the clinical trial evidence for cemiplimab to UK practice (Report sections 3.1.2 and 3.1.3)	Yes	As spelled out in the technical engagement papers, there is now long-term clinical trial data showing responses in >50% out to 60 months. Although the trial evidence is for younger, fitter patients than the UK SACT data, the immature UK SACT data does also show convincing responses with 46% OS at 2 years. We are not aware of any evidence that cemiplimab may be less effective in older patients (3.1.3).
Uncertainty in the clinical effectiveness of best supportive care and chemotherapy (Report section 3.1.5)	Yes	There is perhaps some uncertainty in the outcome for patients receiving BSC in the UK because the great majority of these are managed in the community and patient numbers on which these data are based are low and possibly not representative. However, BSC outcomes in Sun 2019 are consistent with the experience of UK oncologists/clinical experts and help reduce this uncertainty. Similarly, patient numbers were low in the UK chart review and included patients who are not generalisable to those for whom cemiplimab would be considered, but the new data for chemotherapy outcomes do align with that published by Jarkowski 2016, reducing previous uncertainty. However, both the UK chart review and Jarkowski 2016 were small, retrospective, flawed studies with lower median age than both the EMPOWER-CSCC and SACT database; the median survival of 15 months for chemotherapy is longer than would be expected. Many more patients are likely to benefit from immunotherapy than chemotherapy as the use of

		platinum containing chemotherapy is limited to only the fittest patients with adequate renal function.
Uncertainty in the clinical effectiveness of cemiplimab compared with best supportive care and chemotherapy (Report sections 3.1.6 and 3.1.7)	Yes	The 5-year outcome data for cemiplimab from the EMPOWER-CSCC clinical trial are important new data demonstrating durable benefit from cemiplimab despite the 2-year stopping rule. These data show superiority for cemiplimab over either BSC or chemotherapy and the immature data from the SACT review also supports this (see Figure 7).
Baseline characteristics of patients included in the model (Report section 4.2)	Yes	The baseline characteristics of patients in the SACT dataset differed from those in the cemiplimab clinical trials (older, frailer, reduced performance status, higher rates of pre-treatment with more systemic therapy), but they represent real world experience and suggest that the baseline characteristics of patients included in the model are sufficiently generalisable to the UK patient population. These patient differences could partly explain outcome differences.
Uncertainty in the extrapolations of treatment effectiveness for cemiplimab, best supportive care and chemotherapy used in the model (Report sections 4.3 and 4.5)	Yes	The new 5-year, long-term outcome data from the EMPOWER-CSCC clinical trial is extremely helpful in establishing the durability of Cemiplimab responses and removes much of this uncertainty. Chemotherapy does not confer lasting and durable responses. Even if the UK population is older and frailer than the trial population, the immature SACT data at 2 years for cemiplimab are encouraging and suggest that the magnitude of benefit with the RWE data are of the same order as those reported in EMPOWER-SCC clinical trial.
End-of-life criteria (Report section 7) The end-of-life criteria are: • The treatment is indicated for patients with a short life expectancy, normally less than 24 months • There is sufficient evidence to indicate that the treatment offers an extension to life,	Yes	The new data presented herein (SACT dataset, UK Chart review) and the expert opinions/clinical advisory board, support our belief that end-of-life criteria are indeed met. It is important to remember that unlike other human cancers, advanced CSCC is usually a disease of in which loco-regional recurrence is associated with major morbidity prior to death, so the time to death is arguably not the most appropriate measure for patients with this disease. Progression-free survival is a more appropriate measure, but because there is no other effective treatment for CSCC once surgery and radiotherapy have failed, these end-stage patients (for whom cemiplimab is indicated) will usually be just receiving palliative care in the community and PFS will not be documented. Consequently, data on PFS and OS showing the rapid demise of these patients will be missed on the UK

normally of at least an additional 3 months, compared with current NHS treatment		chart review. The experts all agreed that their expectation is for these patients to have died within 6-12 months of starting BSC. Furthermore, the 5-year clinical trial data and the immature SACT dataset confirm a highly significant extension to life with Cemiplimab.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Specialist, real-world clinical experience	General	~~Yes~~/No	[redacted] I have treated 20 patients now since Nov 2018, all of whom would have died within months, often with very painful and advanced local disease. Age range 57-88, all treatment toxicities were manageable. Two patients progressed quickly (both had widespread bone metastases), however, the other 18 have received major benefit from cemiplimab. Two have relapsed after short courses but are still alive. Most would not have been good candidates for chemotherapy. So it is one of the most impressive treatments I have seen in oncology, and I do hope it gets approved.

Additional issue 2: Specialist, real-world clinical experience	General	Yes/~~No~~	[redacted] accepted abstract for a conference presentation: A retrospective case-note review of advanced cSCC in a single tertiary referral centre, treated with cemiplimab between September 2019 and October 2021 was undertaken. Overall, 21 patients received the drug at standard dosing regimens of 350 mg every 3 weeks with a mean cycle duration of 10.3 (range 1–38). Mean age at treatment was 80 y/o (range 59–95 y/o); M:F 19:2. 20/21 cases were high-risk cSCC of head and neck having previously required extensive surgical management with 50% having had adjuvant radiotherapy. Six cases were locally recurrent cSCC and 15 cases were metastatic. Mean follow-up was 16 months (range 5–28 months). Clinical remission was reported in 52% with a sustained response whilst 19% had interval progression on treatment. Mortality rate in our cohort was 33% (7/21), these patients had poor prognostic factors including perineural invasion, chronic lymphocytic leukaemia, metastatic disease and poor performance status. Laboratory abnormalities were reported in 23% (n=5). Two patients discontinued treatment due to immune-related adverse events (notably pneumonitis and hepatitis). In summary, this case series supports cemiplimab use as a successful therapeutic choice for locally advanced and metastatic cSCC, in a clinical setting with minimal treatment options prior to the approval

			of this drug. To the best of our knowledge, this is the first real-world data, presented for a UK cohort which has shown response rates of over 50% at mean follow-up of 16 months with minimal toxicity.

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Evidence Review Group Report commissioned by the
NIHR Evidence Synthesis Programme Programme on behalf of NICE

Cemiplimab for treating cutaneous squamous cell carcinoma (CDF review of TA592) [ID3883]

Evidence Review Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Neelam Kalita Joanne Lord Geoff Frampton
Correspondence to	Geoff Frampton Southampton Health Technology Assessments Centre (SHTAC) Wessex Institute Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	30th March 2022

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Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow

1. Introduction

This document is the Evidence Review Group's (ERG) summary and critique of the response by the company, Sanofi, to the key issues for technical engagement (TE) proposed in the ERG report for this appraisal (submitted to NICE on 3rd March 2022 following the factual accuracy check). The ERG received the company's response on 23rd March 2022.

At the Technical Engagement teleconference the company acknowledged that there was limited new data that they could provide to reduce uncertainty in estimates of cost-effectiveness. The ERG have focused our critique on those issues where the company have provided new data (issues numbered 1, 5 and 7 below).

Table 1 Summary of key issues for technical engagement

Issue number [a]	Summary of issue	Does this response contain new evidence, data or analyses?
1	Generalisability of the clinical trial evidence for cemiplimab to UK practice (Report sections 3.1.2 and 3.1.3)	Yes
2	Uncertainty in the clinical effectiveness of best supportive care and chemotherapy (Report section 3.1.5)	No
3	Uncertainty in the clinical effectiveness of cemiplimab compared with best supportive care and chemotherapy (Report sections 3.1.6 and 3.1.7)	No
4	Baseline characteristics of patients included in the model (Report section 4.2)	No
5	Uncertainty in the extrapolations of treatment effectiveness for cemiplimab, best supportive care and chemotherapy used in the model (Report sections 4.3 and 4.5)	Yes
6	**End-of-life criteria (Report section 7)** The end-of-life criteria are: • The treatment is indicated for patients with a short life expectancy, normally less than 24 months • There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	No

[a] The issues were not numbered in the Technical Engagement template. The ERG have numbered these issues here for ease of referencing. The numbering does not signify priority.

7	**Additional issue**			
	Issue from the ERG report identified by the company	**Relevant section(s) and/or page(s)**	**Does this response contain new evidence, data or analyses?**	**Company's response**
	Differences between original chart review and audit	3.1.5.1 Company chart review: chemotherapy (OS)	Yes	Further details on the differences between the original chart review and audit are presented in **Appendix 4**

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Generalisability of the clinical trial evidence for cemiplimab to UK practice (Report sections 3.1.2 and 3.1.3)

The EMPOWER-CSCC 1 trial included three dose groups (mCSCC 3mg/kg Q2W, laCSCC 3 mg/kg Q2W, mCSCC 350 mg Q3W). The CS stated narratively that response, survival and safety outcomes did not differ among the dose subgroups but no supporting quantitative data were provided in the CS. Quantitative outcomes data have now been provided in Tables 3-10 in the company's response to technical engagement.

The response outcomes reported in technical engagement response Table 3 (stated data cut July 2021) are identical to those reported in clarification response Table 2 (stated data cut October 2020). The ERG are therefore uncertain which data cut the data provided by the company in technical engagement response Tables 3-10 refer to.

As summarised in Table 2 below, response, survival and safety outcomes appear [redacted] between the dose subgroups. However, there is some uncertainty around [redacted] the PFS and OS outcomes between the dose subgroups since confidence intervals are wide (PFS) or inestimable (OS).

Table 2 Summary of Clinical effectiveness and safety data compared across the cemiplimab dose subgroups as provided by the company in response to technical engagement

Company technical engagement response Tables		ERG comments
Response outcomes		
Table 3	Response outcomes (independent central review)	Response outcomes were [redacted] for each dose subgroup. However, these data have already been reported in clarification response Table 2 so are not new. According to clarification response Table 2 the data are from a data cut-off of October 2020, not July 2021 as stated in the technical engagement response.
Table 6	Response outcomes for patients with confirmed pathology (independent central review)	These are new data (not reported in the CS or clarification responses). They show an almost identical picture to those reported in Table 3, i.e[redacted] in response outcomes between the dose subgroups.
Duration of response (DOR)		
Tables 4 and 5	Duration of response (KM estimate)	These are new data (not reported in the CS or clarification responses). Median DOR was [redacted] for the laCSCC 3mg/kg Q2W and mCSCC 350mg Q3W subgroups but was [redacted] for the mCSCC 3mg/kg Q2W dose subgroup.
Survival outcomes		
Table 7	PFS (KM estimate)	These are new data (not reported in the CS or clarification responses). Median PFS was [redacted] across the three dose subgroups, albeit with relatively high uncertainty as indicated by wide confidence intervals.
Table 8	OS (KM estimate)	These are new data (not reported in the CS or clarification responses). Median OS was [redacted] in the mCSCC 350mg Q3W subgroup [redacted] than the mCSCC 3mg/kg Q2W subgroup [redacted] although there is likely to be high uncertainty due to data immaturity (confidence intervals were not estimable).
Safety outcomes		
Tables 9 and 10	Treatment-emergent adverse events (TEAE)	These are new data (not reported in the CS or clarification responses). Overall, [redacted] in the frequencies of all TEAEs or Grade 3/4/5 TEAEs are evident between the dose subgroups. The largest difference in Grade 3/4/5 events between the mCSCC groups was in anaemia ([redacted] in the mCSCC 350mg Q3W subgroup and [redacted] in the mCSCC 3mg/kg Q2W subgroup).

In addition to providing the data for dose subgroups, the company have presented narrative statements on the following issues:

- Cemiplimab is a step change in the treatment of locally advanced and metastatic CSCC patients in the UK. **ERG comment:** No new information has been provided here.

- Patients treated with cemiplimab in the UK are older than those enrolled in the cemiplimab clinical trials. However, the available SACT data is insufficient to reach a definitive conclusion on the generalisability of the cemiplimab trials to UK practice. **ERG comment:** No new information has been provided here.

- Potential impact of COVID-19 on the SACT cohort. **ERG comment:** Most of the information stated here is not new. The company have, however, highlighted a new paper by Challapalli et al. which reports the Named Patient Programme (NPP) study (relevant to ERG Report section 3.1.4). The Challapalli paper suggests that increased awareness of cemiplimab and faster referral may lead to more favourable patient outcomes, which is consistent with the ERG's clinical experts' opinion. The authors of the Challapalli paper concluded that the findings of the NPP were "consistent with the Empower study and other real-world data sets".

- Impact of age. **ERG comment:** The company argue that age may not impact on the efficacy of cemiplimab, citing differences in age and survival between the NPP and SACT datasets and an analysis of a French real-world cohort by Hober et al. We caution that the difference in survival between the NPP and SACT cohorts may not be explained solely by age, since the cohorts differed in other respects such as the proportion with metastatic disease (ERG Report Appendix 3) and relatively limited patient characteristics are available for a detailed comparison. Regarding the Hober cohort, the company had excluded this study from their evidence review because they considered it not to reflect how cemiplimab would be used in NHS clinical practice (CS section A.15.16). Overall, given the limitations of the SACT dataset and the Hober study there is uncertainty in the relationship between patient age and cemiplimab effectiveness.

- ECOG Performance status ≥2. **ERG comment:** No new information has been provided here.

2.2 Issue 2 – Uncertainty in the clinical effectiveness of best supportive care and chemotherapy (Report section 3.1.5)

The company state that uncertainty in the effectiveness of best supportive care and chemotherapy is a result of limitations in the evidence base which cannot be resolved by further analyses or data collection. **ERG comment**: The ERG agree with this interpretation.

For completeness, the company have included data from [redacted] patients in the chart review who received best supportive care and were not originally included in the analysis (technical engagement response Appendix B). The company note that [redacted]". **ERG comment**: Due to the limitations of the data collection process in the chart review it is unclear how reliable the data for these [redacted] patients are. The company had already described the chart review baseline characteristics as having "poor face-validity" (CS section A.15.8).

2.3 Issue 3 – Uncertainty in the clinical effectiveness of cemiplimab compared with best supportive care and chemotherapy (Report sections 3.1.6 and 3.1.7)

The company state that uncertainty in the indirect treatment comparisons is a result of limitations in the evidence base. No new evidence is available so the use of different indirect treatment comparison analysis approaches would not resolve the uncertainty. **ERG comment**: The ERG agree with the company's interpretation.

2.4 Issue 4 – Baseline characteristics of patients included in the model (Report section 4.2)

The company acknowledge that the SACT data supports the suggestion that patients treated with cemiplimab during its time in the CDF were on average older than those in the cemiplimab clinical trials. The company therefore revised their base case to include baseline demographics (mean age and % male) from the SACT data, in line with the ERG's preferred base case. **ERG comment**: The company state that this is a conservative assumption. However, we note that the assumption of an older cohort in the economic model only adjusts the general population caps on mortality and utility. It does not change the survival extrapolations from the clinical trial or comparator data or take account of the greater frailty

of the population treated with cemiplimab in the CDF compared with the population in the company's trials.

2.5 Issue 5 – Uncertainty in the extrapolations of treatment effectiveness for cemiplimab, best supportive care and chemotherapy used in the model (Report sections 4.3 and 4.5)

In Appendix C of their response to technical engagement, the company provided further clarification on their rationale for selecting the survival curves for cemiplimab, chemotherapy and BSC. **ERG comment**: This is helpful but does not resolve the underlying uncertainty associated with the survival extrapolations, which stem from the limited survival data for the two comparator arms and uncertainties over the generalisability of the clinical trial data to the population likely to be treated with cemiplimab in clinical practice.

2.6 Issue 6 – End-of-life criteria (Report section 7)

The company provide a summary of opinion from three additional clinical experts to justify their argument that cemiplimab does meet the end of life criteria in the comparison with chemotherapy, as well as in the comparison with BSC. These experts stated that they would not expect any patients treated with chemotherapy to survive beyond 2-3 years. Based on this view, the company report restricted mean survival for patients on chemotherapy with a maximum survival of 2, 3, 4 and 5 years (Table 1 in the company's response to technical engagement).

The ERG verified the company's restricted mean survival estimates for the revised base case: chart review ATT, trimmed model 1 with loglogistic extrapolation (first row of Table 1 in the technical engagement response). We could not replicate the company's results for the scenario based on Jarkowski et al. data with a Gompertz extrapolation (see Table 3 below). However, the differences between the company and ERG estimates for this scenario are small, and the estimated mean survival remains below two years if maximum survival is restricted to less than 5 years.

Table 3 Chemotherapy restricted mean survival estimates obtained by the company and the ERG: using Jarkowski et al and Gompertz extrapolation (undiscounted)

Maximum survival:	2 years	3 years	4 years	5 years
Company estimates	1.33	1.64	1.86	2.02
ERG estimates	1.29	1.63	1.89	2.09

ERG comment: The validity of the restricted mean survival approach is uncertain and there is a question of whether and how this modification of the survival estimates for the comparator would impact on the cost-effectiveness results.

2.7 Issue 7 – Additional issue – Differences between original chart review and audit

The company have provided additional data showing differences between the original chart review and audit datasets (Appendix D in the company's Technical Engagement Response). The company list several differences including dates of diagnosis (n=9) and dates of follow-up (n=4) among others. The company do not state what proportion of records these differences apply to. Swimmer plots are provided specifically for the chart review UK cohort which show notable differences in the time course of patient responses and line of treatment received between the initial chart review data collection and the audited data. The company have not provided any discussion of these data. **ERG comment**: These new data provided by the company are difficult to interpret given the company's original conclusion in their CS that the chart review data have poor face-validity.

3. Updated cost-effectiveness results - ERG summary and critique

The company have accepted the ERG's preferred model as their revised base case, which results in an ICER of £37,775 for cemiplimab versus chemotherapy and £30,952 for cemiplimab versus BSC, respectively. No other changes were made.