NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma [ID1367]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma [ID1367]

Contents:

The final scope and final matrix are available on the NICE website

10. **Evidence Review Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessments Centre (SHTAC)

11. **Final Technical Report**

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

Single technology appraisal

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

Document B

Company evidence submission

25 October 2018

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Contents

Tables and figures

B.1. Decision problem, description of the technology and clinical care pathway

- Cutaneous squamous cell carcinoma (CSCC) is a distinct form of non-melanoma skin cancer (NMSC). It is characterised by a high mutational burden secondary to UV exposure[1] and represents around 23% of all NMSCs.[2]
- In the majority of cases (~95%) CSCC is curable by surgery, however in a small proportion of patients the tumour reaches an incurable advanced state.[3] This includes patients with locally advanced disease (laCSCC), who are not candidates for surgery or curative (radical) radiotherapy, and metastatic disease (metastatic cutaneous squamous cell carcinoma [mCSCC]).
- Although in patients with primary CSCC, 3-year disease-specific survival rate is 85%[4], the European Dermatology Forum guidelines have reported a median overall survival (OS) in CSCC patients with distant metastasis of less than 2 years[5]. In addition, a retrospective chart review demonstrated a median OS of just 15.1 months in advanced CSCC patients receiving platinum-based chemotherapy.[6]
- As CSCC advances, lesions can grow very large, spread to different parts of the body and result in disfigurement and burdensome symptoms such as pain and pruritus.[7-9] This can lead to a reduced quality of life (QoL), affecting psychological health and social relationships.[10]
- There are currently no licenced systemic treatment options specific to advanced CSCC and, as such, no optimal treatment for advanced CSCC.[5] As a result clinicians currently offer best supportive care (BSC) or rely on off licence treatments with limited or anecdotal evidence in advanced CSCC.
- The majority of advanced CSCC patients in the UK receive BSC (~75%). Off licence platinum-based chemotherapy is used in patients considered fit enough to tolerate it (~25%).
- There is a high unmet need for a licenced, tolerable treatment with substantial and durable tumour shrinkage and potential for long-term survival in patients with advanced CSCC.
- Cemiplimab (Libtayo®) is a human monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thus facilitating normal T-cell mediated cytotoxic activity.[11]
- Checkpoint inhibitors such as PD1 inhibitors have changed the treatment landscape for many cancers where by facilitating an anti-tumour immune response such therapies have led to highly durable responses and long term survival in a proportion of patients.[12]
- Cemiplimab will be the first licenced systemic treatment for advanced CSCC.

B.1.1. Decision problem

The submission covers the technology's full anticipated marketing authorisation for this indication. The decision problem addressed within this submission is presented in Table 1.

Whilst the data for cemiplimab look very promising, the anticipated marketing authorisation will be based on data from a Phase I and a Phase II single arm clinical trial, Sanofi acknowledges the following limitations in the context of demonstrating clinical and cost-effectiveness:

- Advanced CSCC patients have a poor prognosis and there are no approved treatment options available for these patients
- Data available at the time of this submission is early and based on a follow-up of less than 1 year
- Both studies were non-randomised with no comparison of cemiplimab to current treatments. The difficulties in conducting a randomised Phase III study is further discussed in Section B.2.13.
- Data for cemiplimab is based on a small population with 108 patients in the efficacy analysis and 163 in the safety analysis; nevertheless, these 163 patients represent the largest prospective dataset in advanced CSCC.

Given these limitations and the resulting uncertainty Sanofi is conscious that the committee may want to consider a recommendation for cemiplimab to be made available via the CDF whilst further data are collected. It is anticipated these key areas of clinical uncertainty will be reduced with mature data from the currently ongoing cemiplimab trial programme (for detailed timelines see Section B.2.11) as well as results from a planned retrospective, observational study. In addition, routinely captured data from the Systemic Anti-Cancer Therapy Dataset (SACT) could be used to provide further information on treatment with cemiplimab in the UK.; Further details of this proposed data collection are provided in Appendix O.

As a treatment for advanced CSCC, cemiplimab also satisfies the end-of-life criteria. The base case cost-effectiveness results, alongside a proposed commercial access agreement (CAA) demonstrate plausible potential for cemiplimab to satisfy the criteria for routine commissioning.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma in whom there is no curative local therapy.	People with metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiotherapy.	The population included in this appraisal is in line with the scope. The base case is focused on the overall population (i.e. both metastatic and locally advanced CSCC), termed the 'advanced CSCC' population.
Intervention	Cemiplimab	Cemiplimab	NA
Comparator(s)	• Best supportive care • Chemotherapy (such as platinum-based chemotherapy and fluorouracil)	• Best supportive care • Chemotherapy (such as platinum-based chemotherapy and fluorouracil)	NA
Outcomes	• Progression-free survival • Overall survival • Response rate • Duration of response • Adverse effects of treatment • Health-related quality of life	• Progression-free survival • Overall survival • Response rate • Duration of response • Adverse effects of treatment • Health-related quality of life	NA
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness	As per reference case.	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Key: CSCC, cutaneous squamous cell carcinoma; NA, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service.			

B.1.2. Description of the technology being appraised

A description of cemiplimab is presented in Table 2. The draft summary of product characteristics (SmPC) is presented in Appendix C. The European Public Assessment Report (EPAR) will be available at a later date.

Table 2: Technology being appraised

UK approved name and brand name	Cemiplimab (Libtayo®)
Mechanism of action	Cemiplimab is a 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 ligand PD-L1 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. Checkpoint inhibitors such as PD1 inhibitors have changed the treatment landscape for many cancers where by facilitating an anti-tumour immune response such therapies have led to highly durable responses and long term survival in a proportion of patients.[12] There is also now compelling evidence that patients continue to respond to PD-1 treatments after treatment discontinuation which is suggestive of a reprogramming of the immune system.[13, 14]
Marketing authorisation	[redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is: "*Cemiplimab as monotherapy is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery.*"

Method of administration and dosage	Administration is via 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 anticipated licenced dose of cemiplimab is a dose of 350mg every three weeks. Treatment may be continued through initial measurable disease progression until symptomatic disease progression or unacceptable toxicity.
Additional tests or investigations	No additional tests or investigations are needed.
List price and average cost of a course of treatment	The list price for cemiplimab will be [redacted] per 350mg vial. With a dosing regimen of 350mg every three weeks, [redacted] is also the cost of cemiplimab per treatment cycle. Patients will be treated with cemiplimab until progression. The cost for a year of treatment with cemiplimab based on the list price is [redacted].
Patient access scheme (if applicable)	[redacted]

Key: CDF, Cancer Drugs Fund; CHMP, Committee for Medical Products for Human Use; CSCC, cutaneous squamous cell carcinoma; EMA, European Medicines Agency; IgG4, immunoglobulin G4; PAS, patient access scheme; PD-1, programmed cell-death 1; PD-L1, programmed cell-death 1 ligand; SmPC, summary of product characteristics.
Source: Draft SmPC, 2018.[11]

B.1.3. Health condition and position of the technology in the treatment pathway

Disease background

Non-melanoma skin cancer (NMSC) is the most common group of cancers in the UK and Ireland, accounting for roughly 20% of all new malignancies and 90% of all skin cancers registered.[2] Cutaneous squamous cell carcinoma (CSCC) is the second most common form of NMSC after basal cell carcinoma (BCC), representing around 23% of all cases.[2] Although rare, advanced stages of CSCC are attributed to more deaths than any other form of NMSC[15] and may even approach mortality similar to that from melanoma, particularly in geographic areas with high exposure to UV radiation.[16]

CSCC develops from keratinocyte cells in the epidermis of the skin which typically have had high exposure to the sun.[17] Ultraviolet (UV) radiation from the sun is thought to be the major driver in the development of CSCC[2], causing damage to cellular and molecular structures including DNA. Incomplete repair of damaged DNA can lead to an accumulation of mutations within a cell that ultimately, if left unchecked, can progress and transform into CSCC.[1] As such there a higher risk of CSCC in people who work outdoors.[18]

In the majority of cases (~95%) CSCC is curable by surgery and or radiation, however, in a small proportion of patients the tumour reaches an incurable advanced state.[3] Advanced CSCC, the population of interest to this submission, includes patients with metastatic disease (mCSCC) and patients with locally advanced disease (laCSCC) who are not candidates for surgery or curative radiotherapy. In this context:

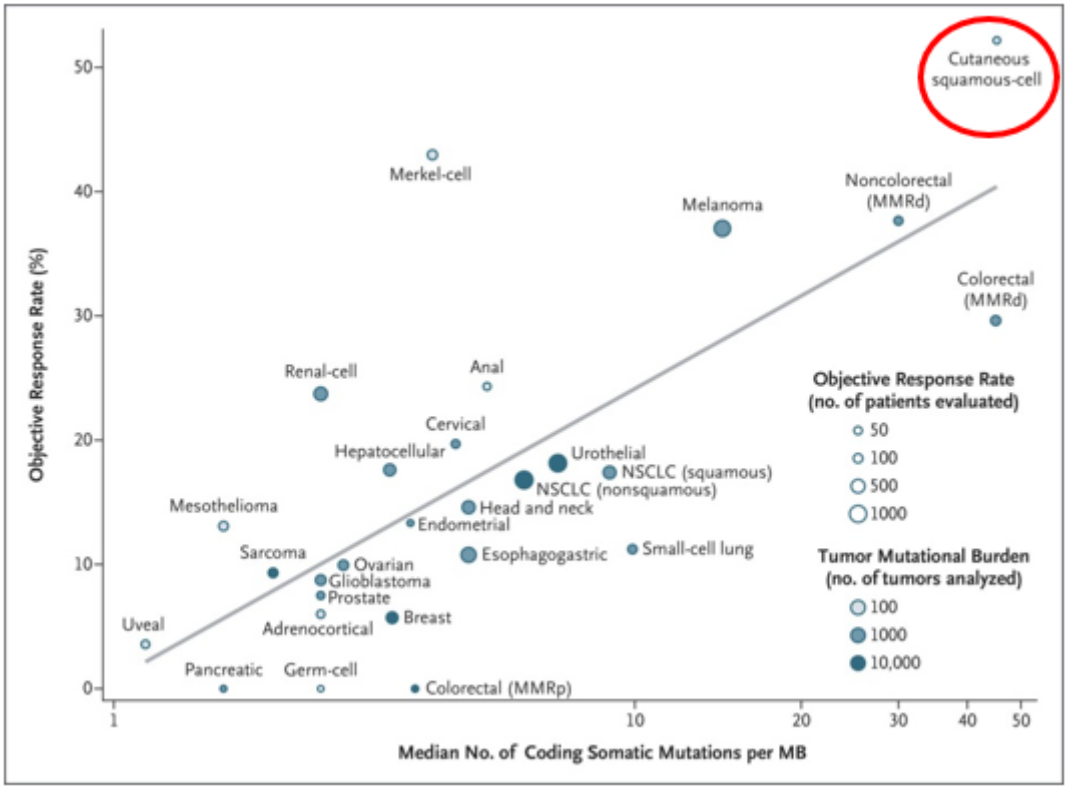
- mCSCC primarily involves the spread of tumours to regional lymph nodes (~85% of cases) or distant spread to other organs of the body (~15% of cases).[5]
- laCSCC are patients with tumours that have invaded the deeper layers of the skin or surrounding structures, are typically aggressive or recurrent who are not candidates for curative surgery or curative radiotherapy. [3, 19]

Patients with advanced disease are therefore classified as incurable by surgery and or radiation. With no present licensed systemic treatment options available, there is considerable unmet need in the treatment of advanced CSCC.[3]

Defining these separate patient populations, i.e. laCSCC and mCSCC, is challenging due to a lack of consensus guidelines segmenting this population. Where guidelines do exist, they often use different criteria to stage the disease which often overlap, lack extensive validation and have limited prognostic utility.[20-22] Due to this, treatment approaches are the same for both populations and in clinical practice these patients are treated as one population. As such, patients with either mCSCC or laCSCC who are not candidates for curative surgery or radiation can be justifiably grouped together and treated for 'advanced CSCC'.

It is important to note that CSCC is a distinct disease and separate to both melanoma, other NMSCs and other squamous cell carcinomas (SCCs) such as head and neck squamous cell carcinoma (HNSCC). CSCC has the highest known mutational burden (a measure of the level of mutations in a cancer cell) of any squamous cancer and carries four times the rates seen in melanoma.[1] There is a strong correlation emerging between the response rate of immunotherapy (specifically inhibitors of the PD-1/PD-L1 pathway) and tumour mutational burden as shown in Figure 1.[23] Advanced CSCC therefore has the clinical and molecular hallmarks of a tumour likely to be responsive to immunotherapies.[23, 24]

Figure 1: Correlation between tumour mutational burden and overall response rate with anti-PD-1 or anti-PD-L1 therapy



Key: MB, megabase; MMRd, mismatch repair-deficient; MMRp, mismatch repair-proficient; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1.
Source: Yarchoan *et al.* 2017.[23]

Aetiology, course and prognosis

CSCC is more prevalent among Caucasians, males and patients over 65 years of age[25], although younger populations are becoming increasingly at risk.[26] The major risk factors for CSCC are exposure to UV radiation from the sun or sunbeds especially for fair skinned people, advanced age and immunosuppression.[2, 27] For patients who have received a solid organ transplant and/or are receiving immunosuppressive drugs, there is a 65- to 250-fold greater CSCC incidence compared to the general population.[3, 27]

Although CSCC is cured in the majority of patients, in a small proportion of patients the tumour reaches an incurable advanced state.[3] These advanced patients are often older and have a poor prognosis; lymph node involvement is associated with

increased risk of recurrence and mortality[5], with rates of metastases typically around ~16%.[4] Although in patients with primary CSCC, 3-year disease-specific survival rate is 85%[4], the European Dermatology Forum guidelines have reported a median overall survival (OS) in CSCC patients with distant metastasis of less than 2 years[5]. In addition, a retrospective chart review demonstrated a median OS of 15.1 months in advanced CSCC patients receiving platinum-based chemotherapy.[6]

Advanced CSCC patients have a short life expectancy in line with the end-of-life criteria defined by NICE (further discussed in Section B.2.13).

Epidemiology

Incidence of CSCC is not well documented and accurate epidemiological data are lacking.[28] Moreover, there are large variations between different sources.[28] This is largely attributed to data sources pooling data across different skin cancers, with many registries and national databases such as the Hospital Episode Statistics (HES) not distinguishing between the different forms of NMSCs or between patients at each stage of disease progression. As a result, there are significant challenges in defining the epidemiology of CSCC, not just for the total population but within each disease stage too: localised, locally advanced and metastatic.

In a retrospective analysis of all cases of primary CSCC on the Isle of Wight between 2005 and 2014 average incidence was 112 patients per year in a population of 138,392 (81 per 100,000).[29] When applied to the population of England in 2018 this indicates an incidence of 45,358 patients.[30] Based on this figure alongside clinical opinion on the proportion of non-immunocompromised advanced CSCC patients who would be eligible for systemic treatment, approximately 650 patients per year are estimated to be eligible for systemic treatment in England. However, these figures should be interpreted with caution given the scarcity of available data, and that this may be an overestimate both due to the typically older population and sunny climate of the Isle of Wight and that a panel of UK clinical experts estimated there are approximately 250 new patients with advanced CSCC in England each year.

Burden of disease

The first sign of CSCC typically includes a non-healing ulcer or abnormal growth in primary sun exposed areas or a shallow ulcer with heaped-up edges, often covered by a plaque.[9] Patients typically undergo surgery in the first instance, which is curative in over 95% of cases[3] However, recurrence rates can be higher for certain locations such as the head and neck, and for tumours greater than 2cm in size.[31] Surgery can also result in various complications including scarring, disfigurement and functional loss.[32] Numerous complications can occur in the eyes and nose, often resulting in older patients being unable to wear glasses and hearing aids.[32] In addition, locally advanced lesions can encroach on critical facial structures, making further surgical resection medically inadvisable and can have a significant risk of disfigurement.

As the disease progresses, lesions may grow quite large and spread to different parts of the body, including adipose tissues, cartilage, muscle and bone.[22] Perineural invasion (where the tumour spreads into the space surrounding a nerve) is often clinically occult[22] (concealed) but can result in pain, itching, numbness and tingling[7] and is associated with poor outcomes for CSCC.[5] Significant perineural invasion can lead to cranial nerve dysfunction, most often involving the facial and trigeminal nerve.[9]

Although there is limited data on the emotional and psychological effects of skin cancer, the potentially disfiguring nature of advanced CSCC for patients, as presented in Figure 2, can have a large negative impact on the patient's quality of life (QoL). Visual disfigurement, particularly around the head and neck, can have a far-reaching impact, including reduced self-confidence, low self-esteem, difficulty with social interactions and social withdrawal.[10, 33] Patients with disfigurement due to cancer and its treatments have been shown to have a reduced QoL, affecting physical and psychological health and social relationships.[10]

The impact on QoL posed by advanced CSCC may arise from the visual impact of the tumour itself, or as a result of treatment through symptoms, functional limitations, cosmetic burden and additional considerations such as cost and disturbance to the activities of daily living.[34]

Figure 2: Visual example of patients with advanced CSCC

Notes: The left-hand image shows a 62-year-old patient with advanced CSCC, whilst the right-hand image shows an 83-year-old patient who had undergone multiple surgeries for CSCC.
Source: Migden *et al*. 2018.[3]

Patients are often stigmatised for appearing different than 'normal' and may be considered 'dysfunctional' by others.[35] Patients with facial disfigurements have been reported to have similar levels of socially phobic and agoraphobic avoidance to socially phobic patients.[36] A market research conducted by Sanofi further suggests patients with advanced CSCC often experience feelings of isolation, ignorance and powerlessness, with patients commenting:

"*I have resigned myself to accepting the fact that I basically no longer have a nose and I am in constant pain*"

"*I haven't had anyone to talk to. I can talk to my wife but I don't want to burden her…I haven't told anyone about the cancer – I couldn't stand pity from others*"

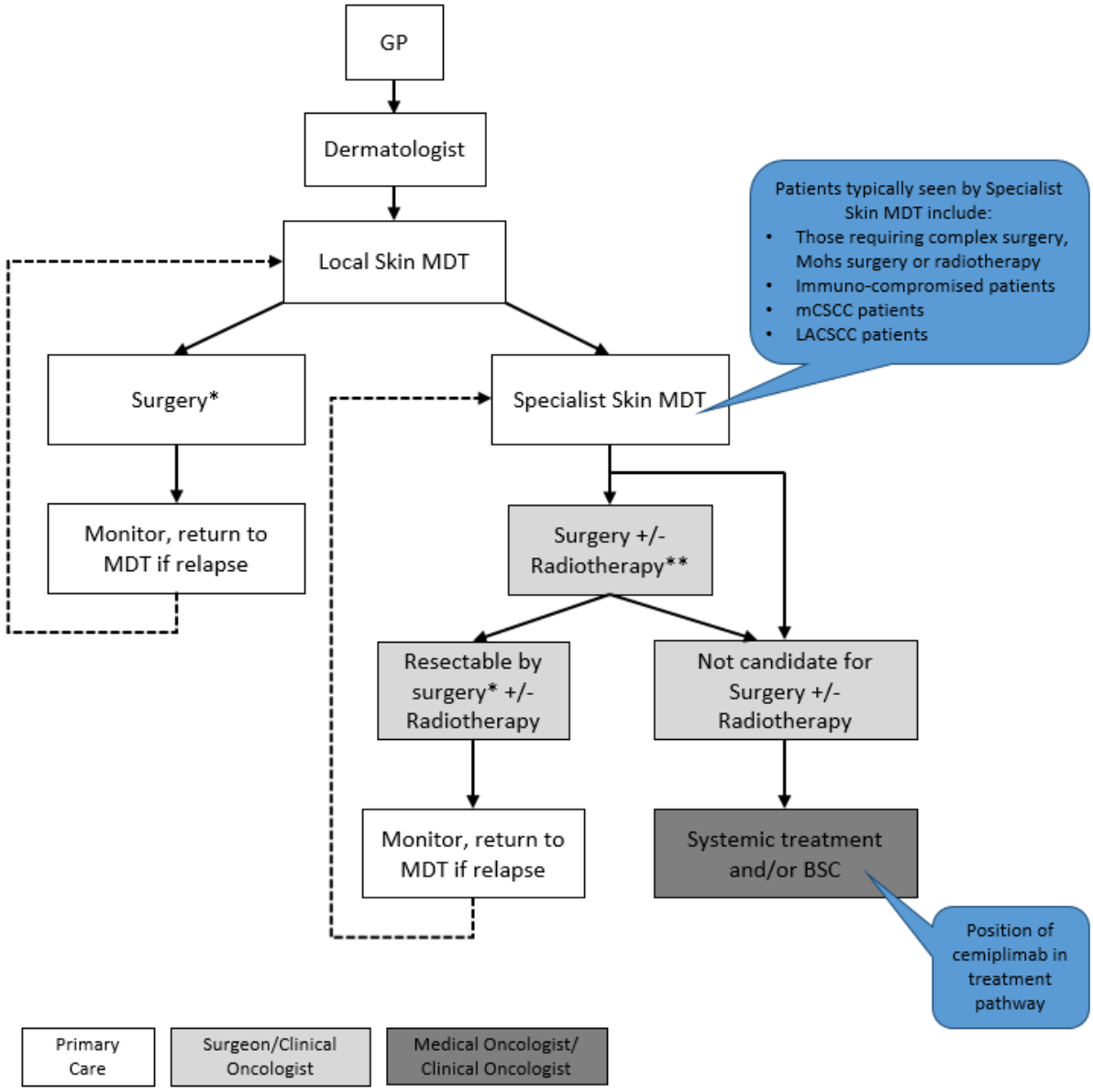
Finally, there is a substantial economic burden associated with the current treatment of advanced CSCC. A US-based study demonstrated that patients with metastatic or locally advanced NMSCs are two to three times more costly to the healthcare

system, calculated based on the total of per-patient per-month (PPPM) costs, than other NMSC patients respectively, with resource use and cost increasing as the disease advances.[37]

Current pathway of care

The treatment pathway for CSCC in the UK is summarised in Figure 3 below. The first sign of CSCC typically includes a non-healing or shallow ulcer, or abnormal growth in primary sun exposed areas.[9] In the UK, patients are typically referred from primary care via a dermatologist to a local skin cancer multidisciplinary team (MDT), consisting primarily of dermatologists and surgeons. Surgical resection is the mainstay of clinical management for patients with localised disease and is curative in over 95% of cases.[3] These patients are monitored, and in case of relapse they are re-referred to the local skin MDT.

Figure 3. CSCC treatment pathway



Key: BSC, best supportive care; CSCC, cutaneous squamous cell carcinoma; GP, General Practitioner; LACSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; MDT, multidisciplinary team.
Notes: *, successful single surgical procedure in ~95% of cases, confirmed by pathology; **, where there is a narrow or positive margin, confirmed by pathology, radiotherapy is often used.

Clinical experts advised that more complex or high-risk cases are typically referred on from the local skin MDT to a specialist skin MDT, which typically comprises a dermatologist, surgeons (plastics, head and neck, maxillary facial, Mohs),

pathologist, radiologist, oncologists and specialist nurses. Patients include those requiring more complex or Mohs surgery, immunocompromised patients, patients with metastases or those requiring radiotherapy.

Whilst some locally advanced patients will remain candidates for further surgery, a proportion will be considered as inoperable - for example, locally advanced lesions can encroach on critical facial structures, making further surgical resection medically or cosmetically not preferable. Others may have a medical contraindication to surgery or radiation, or be unlikely to achieve disease control with these treatments.[19] Such patients are considered high risk for local recurrence or metastasis. Metastatic disease primarily involves the spread of tumours to regional lymph nodes (~85% of cases) or distant spread to other organs of the body (~15% of cases).[5] Patients with more complex disease, including those with incurable advanced CSCC, are typically referred to a specialist skin cancer MDT and are managed by a clinical or medical oncologist.

For patients with advanced CSCC, there are currently no approved systemic therapies and, therefore, there is a high unmet need. Clinicians rely on unlicensed treatments with limited supporting evidence such as platinum-based chemotherapy, (usually cisplatin + 5-Flurouracil [5-FU]), which show only modest efficacy and are limited by associated toxicities.[5, 6]

In a UK advisory board conducted by Sanofi, clinical oncologists indicated that 75% of advanced CSCC patients would receive best supportive care (BSC) as they would be considered unsuitable for treatment with chemotherapy. Given this population is characterised by advanced age and multiple comorbidities, these patients would not be considered fit enough to tolerate chemotherapy. BSC consists of palliative care to manage symptoms. This could include palliative radiotherapy (RT), palliative surgery, analgesics and extensive wound management.

According to clinical opinion, the remaining 25% of advanced CSCC patients are candidates for platinum-based chemotherapy (usually cisplatin + 5-Flurouracil [5-FU]). Platinum-based chemotherapy along with other targeted systemic therapies have only been described in small case series or studies reporting a small number of

patients. In most cases, the efficacy of these treatment options is supported only by retrospective case review studies.[6, 38, 39]

A retrospective chart review, conducted by Jarkowski et al in the USA in 2016, has demonstrated a median overall survival (OS) of 15.1 months in advanced CSCC patients receiving platinum-based chemotherapy.[6] As highlighted above the use of chemotherapy in the advanced CSCC population is limited by its toxicity. Although some patients do respond to chemotherapy clinicians have indicated that many patients discontinue treatment due to adverse events which can be unpredictable and difficult to manage in this patient group. Common side effects include an increased risk of infection, fatigue, nausea and vomiting, diarrhoea, anaemia, haematological problems, kidney damage and hearing issues.[40]

Chemotherapy regimens offer limited durable efficacy and pose challenges in terms of toxicity management, particularly in older populations, limiting its use in most advanced CSCC patients.[5, 27]

Unmet need

Patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation represent an older, co-morbid population that has exhausted treatment options and suffers from substantial morbidity and a high mortality rate. Due to a lack of consensus guidelines, these patients are treated as one population, termed ‘advanced CSCC’. There are currently no approved systemic therapies for this population. Instead, clinicians rely on treatments with limited supporting evidence based on small patient populations which have shown only modest benefits and have known risks.[5]

Advanced CSCC and its treatments may result in severe disfigurement and pain, significantly impacting patient burden and may reduce patient QoL, affecting physical and psychological health and social relationships.[10, 22, 32, 34, 36]

Checkpoint inhibitors such as PD1 inhibitors have changed the treatment landscape for many cancers where by facilitating an anti-tumour immune response such therapies have led to highly durable responses and long term survival in a proportion

of patients.[12] There is also now compelling evidence that patients continue to respond to PD-1 treatments after treatment discontinuation which is suggestive of a reprogramming of the immune system.[13, 14]

Cemiplimab will be the first approved systemic treatment for advanced CSCC, demonstrating substantial and durable levels of response in the largest clinical trial patient population of its kind in advanced CSCC. Cemiplimab is generally well tolerated with a well characterised AE profile, comparable to currently used PD-1 inhibitors.[3]

B.1.4. Equality considerations

Patients with advanced CSCC are often older, with the average age of patients in the cemiplimab trials being 70 years.[41] There is growing evidence that older patients with cancer may be under treated and that age is a significant factor in clinical decision making.[42] Although age is associated with factors such as comorbidities and frailty that may legitimately influence treatment decisions, as life expectancy increases many older people are healthier than they would have been in previous generations. It is therefore important that the decision regarding treatment for advanced CSCC is not solely based on a patient's age.

B.2. Clinical effectiveness

- The key clinical data on the effectiveness and safety of cemiplimab is derived from an integrated analysis of a Phase I and Phase II study in adult patients with advanced CSCC. These two studies provide the largest prospective data set in advanced CSCC, enrolling a total of 163 patients.
- Cemiplimab is associated with substantial and durable tumour shrinkage, demonstrated by an objective response rate (ORR) of [redacted]%.[41] Importantly, [redacted]% of advanced CSCC patients saw a benefit while on treatment. [redacted]% of patients achieved a duration of response (DoR) greater than 6 months with overall time to response (TTR) of [redacted].
- After a median follow-up of 9 months, both OS and progression-free survival (PFS) were [redacted]; 12-month event-free rates were [redacted]% and [redacted]%, respectively.[41]
  - Efficacy with cemiplimab was demonstrated across all subgroups, including [redacted]. No subgroup analyses demonstrated clinically meaningful differences.
- Treatment with cemiplimab also improved patients' pain levels when measured by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core-30 (QLQ-C30). This reduction may be considered clinically meaningful.[43]
- Naïve and population adjusted comparisons suggest that cemiplimab [redacted]
- Cemiplimab was generally well tolerated with rates of Grade [redacted].[44]
- Only [redacted] of patients discontinued treatment due to AEs. Furthermore, [redacted] of patients reported an immune-related adverse event (irAE), [redacted][44]
- Cemiplimab will be the first PD-1 inhibitor and only approved systemic treatment available for advanced CSCC patients.
- Cemiplimab has shown substantial and durable tumour shrinkage with good tolerability and a low rate of SAEs. Cemiplimab has the potential to relieve the significant disease and patient burden seen with advanced CSCC alongside the potential to significantly improve survival in this population.

-

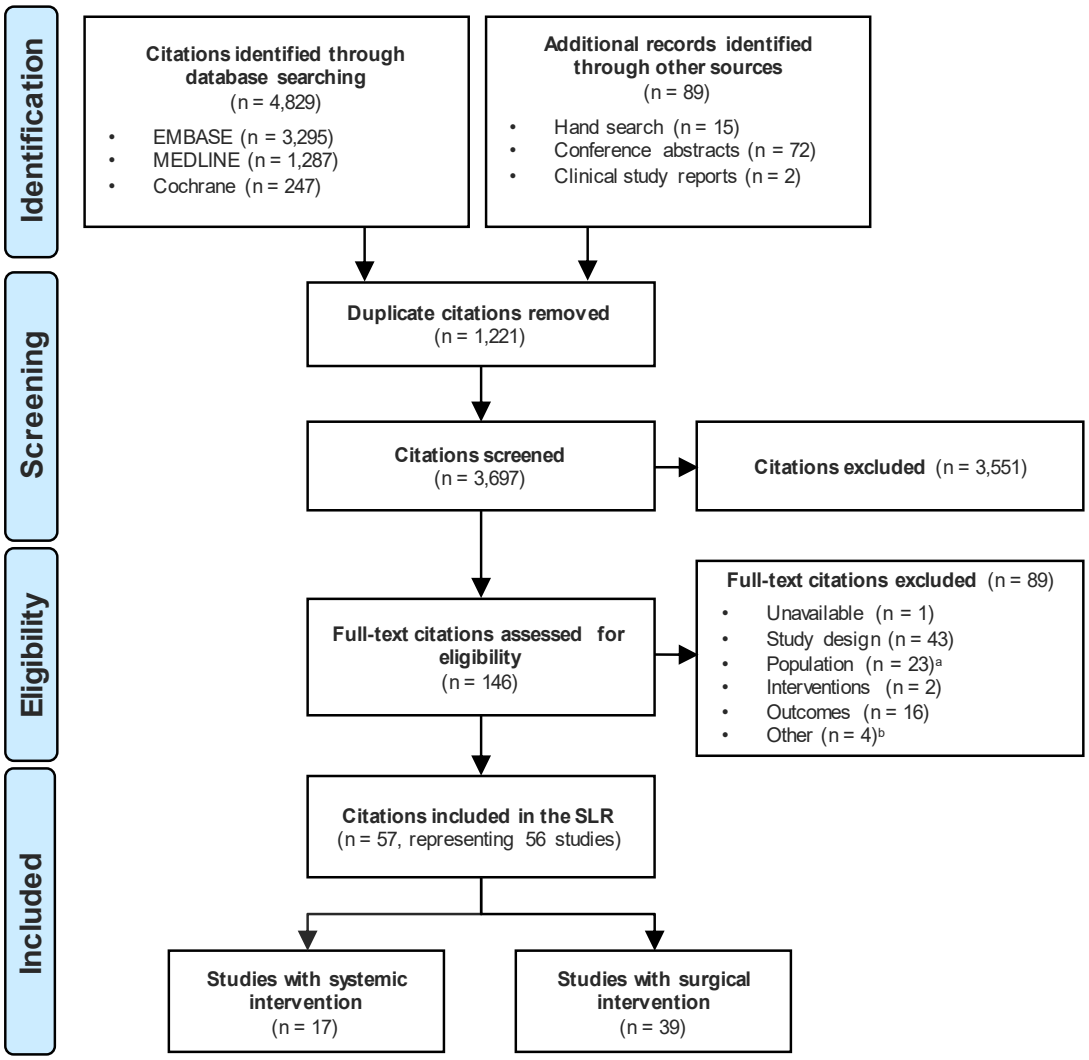
B.2.1. Identification and selection of relevant studies

A full systematic literature review (SLR) was performed in October 2017 to identify studies that investigated the efficacy and safety of treatments for patients with advanced CSCC. The searches were subsequently rerun in September 2018 with no new studies of relevance to the decision problem identified. Relevant studies were identified through searches of Embase, MEDLINE and Cochrane Central Register of

Controlled Trials (CENTRAL), as well as hand searches of relevant conference proceedings and online resources such as clinicltrials.gov.

A total of 4,829 citations were identified and, after primary and secondary screening, 57 citations, corresponding to 56 studies, were included in the final review. Of these only 17 studies featured systemic therapies, with 39 featuring surgical interventions. No randomised controlled trials (RCTs) were identified that met the eligibility criteria of the review. Of the 17 studies of systemic interventions, only three were relevant to the decision problem: two studies of cemiplimab (described in the following sections) and one of chemotherapy (described in Appendix D.1.3.4). Literature search results are summarised in Figure 4.

Figure 4: PRISMA flow diagram of literature search results



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D.1.

B.2.2. List of relevant clinical effectiveness evidence

The SLR identified two non-randomised, prospective studies that provided evidence on the clinical benefits of cemiplimab, as summarised in Table 3.

- An open-label, multicentre Phase I study in patients with a variety of advanced solid tumours, including patients with mCSCC or laCSCC who were not candidates for surgery.
- An open-label, multicentre Phase II study (EMPOWER-CSCC 1) in adult patients with mCSCC or laCSCC who were not candidates for surgery.

No comparative studies of cemiplimab were identified, therefore comparisons to current standard of care were conducted through an ITC, as presented in Section B.2.9.

Table 3: Clinical effectiveness evidence

Study	Phase I Study (NCT02383212)					Phase II EMPOWER-CSCC 1 (NCT02760498)				
Study design	Phase I, open-label, non-comparative, multicentre study.					Phase II, non-randomised, non-comparative, three-group, multicentre study.				
Population	Adults with advanced solid tumours, including cohorts of patients with mCSCC or laCSCC who were not candidates for surgery.					Adults with mCSCC or laCSCC who were not candidates for surgery.				
Intervention(s)	Cemiplimab 3mg/kg IV q2w					Cemiplimab 3mg/kg IV q2w until progression or up to 96 weeks (22 months). Cemiplimab 350mg fixed dose IV q3w until progression or up to 54 weeks[a]				
Comparator(s)	N/A					N/A				
Indicate if trial supports application for	Yes	X	**Indicate if trial used in the**	Yes	X	Yes	X	**Indicate if trial used in the**	Yes	X
	No			No		No			No	

Study	Phase I Study (NCT02383212)	Phase II EMPOWER-CSCC 1 (NCT02760498)
marketing authorisation	**economic model**[b]	**economic model**[b]
Rationale for use/non-use in the model	Supportive study in a wider patient group; provides longer-term follow-up data for the advanced CSCC cohort.	Pivotal study supporting this indication.
Reported outcomes specified in the decision problem	• ORR • DoR • **PFS** • **OS** • **Safety**	• ORR • DoR • **PFS** • **OS** • **Safety**
All other reported outcomes	N/A	• HRQL measured by EORTC QLQ-C30

Key: DoR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core-30; HRQL, health-related quality of life; IV, intravenous; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; N/A, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks.
Notes: [a], enrolment for this group is not yet completed and therefore results are not presented; [b], both studies were pooled and comprised the integrated analysis; this integrated analysis was then used in the economic model.
Source: Migden *et al*. 2018[3]; Phase II EMPOWER-CSCC 1 CSR, 2018[45]; Phase I study CSR, 2018.[46]

Integrated analysis

Initial study results from the Phase I study suggested cemiplimab is highly effective in both mCSCC and laCSCC and that there was a need to bring this new treatment to patients as soon as possible.[47] As such, a decision was taken to pool the data from the two studies to provide an integrated analysis. This formed the basis of the EMA submission. This represents the most robust and precise assessment of efficacy in the advanced CSCC populations and provides the largest prospective data set in advanced CSCC, enrolling a total of 163 patients.

UK clinicians agreed that data from the two trials should be pooled because the eligibility criteria are highly similar (see Table 4). Clinicians also agreed that, despite the small patient population of the Phase I study, this provides longer follow-up and could therefore increase the power of the data.

As previously discussed in Section B.1.3, the population enrolled in the two studies represents the advanced CSCC population, that is patients with metastatic or locally advanced CSCC who are unsuitable for surgery and who currently have no treatment options. Pooling these two populations was considered appropriate for the following reasons:

- Given the immaturity of the data and the small patient numbers for the different subgroups in the Phase II trial, it was considered unfeasible to present meaningful results based on subgroup analyses.
- UK clinical experts attending an advisory board suggested it would be reasonable to pool these subgroups together given that patients at this late stage of disease would be treated in the same way.
- Efficacy data for comparator treatments in advanced CSCC is limited. Only one study was identified through the SLR for chemotherapy and this included only data for a mixed cohort of advanced CSCC patients. It would therefore be unfeasible to conduct a population-adjusted indirect treatment comparison (ITC) for each subgroup separately given the available published evidence.

In addition, data from both the Phase I and Phase II EMPOWER-CSCC 1 studies were pooled. UK clinicians agreed that data from the two trials should be pooled because the eligibility criteria are highly similar (see Table 4). Clinicians also agreed that, despite the small patient population of the Phase I study, this provides longer follow-up and could therefore increase the power of the data.

Further information on the pooled integrated dataset is discussed in Section B.2.3.1.3.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Study design

B.2.3.1.1. Phase I study

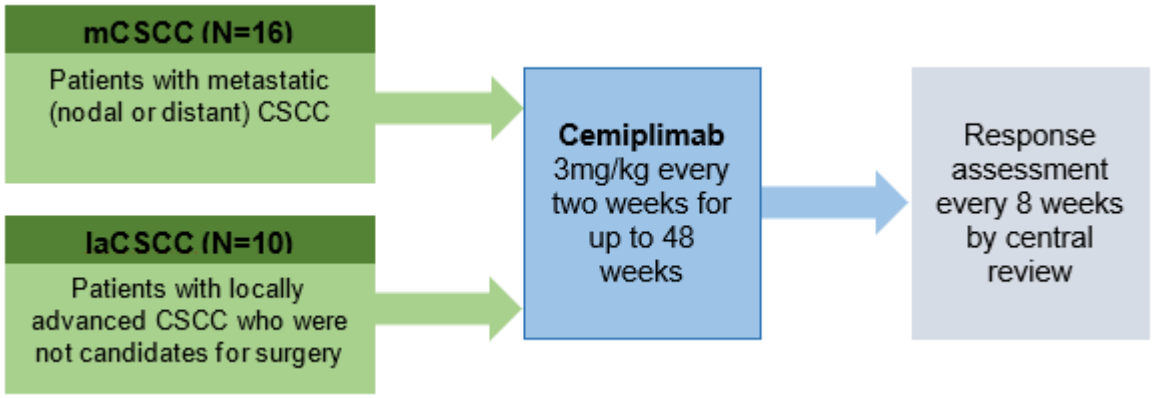
The Phase I study (Study 1423) is a first-in-human, open-label, multicentre study of cemiplimab in patients with solid tumours, including two expansion cohorts of

patients with mCSCC and laCSCC who are not candidates for surgery.[3] This study is a supporting trial for this indication and was included in the regulatory file (see Section B.2.3.1.3); the median follow-up for CSCC patients was 11.1 months (range: 1.1–17).[47]

Key eligibility criteria included Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, adequate organ function and the presence of at least one lesion that could be measured according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[3] Patients received a 30 minute infusion of cemiplimab at 3mg/kg every two weeks for up to 48 weeks. The primary objective of the study was to characterise the safety and side effect profile of cemiplimab and secondary endpoints include DoR, PFS and OS.

A study design schematic is presented in Figure 5.

Figure 5: Study design schematic, Phase I study



Key: CSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma.

B.2.3.1.2. Phase II EMPOWER-CSCC 1

The Phase II EMPOWER-CSCC 1 study is an ongoing Phase II, non-randomised, three-group, multicentre study evaluating the efficacy and safety of cemiplimab in patients with advanced CSCC, defined as patients with mCSCC or laCSCC who are not candidates for surgery.[3] The Phase II EMPOWER-CSCC 1 study is one of the pivotal trials supporting this indication, providing a median patient follow-up of 8.6

months,[47] and was used in the regulatory submission. The trial was conducted at 31 sites in the US, Australia and Germany.

The study enrolled patients with mCSCC (Group 1) or laCSCC who are not candidates for surgery (Group 2) to receive cemiplimab 3mg/kg every two weeks for up to 96 weeks.[3] After completion of Group 1 enrolment, the protocol was amended to include a third group of patients with mCSCC who would receive 350mg fixed dose cemiplimab every three weeks (Group 3).[41] Efficacy data for this group are not yet available and therefore not included within the efficacy analysis for this submission. Nevertheless, the majority of the data supporting the marketing authorization for cemiplimab are derived from patients who received the 3mg/kg q2w dosing regimen. Safety and efficacy data from this 3mg/kg q2w regimen are used to support the proposed dose regimen (350mg q3w) based on pharmacokinetic (PK) modelling and simulation of exposure, and supported by observed data at 350mg q3w. The population PK analyses demonstrate that the 350mg Q3W regimen, which has the advantage of less frequent dosing, achieves exposure and between-patient variability similar to the 3mg/kg q2w dosing regimen; this is further discussed in B.2.13. Additional data collection at the 350mg q3w dose is ongoing.

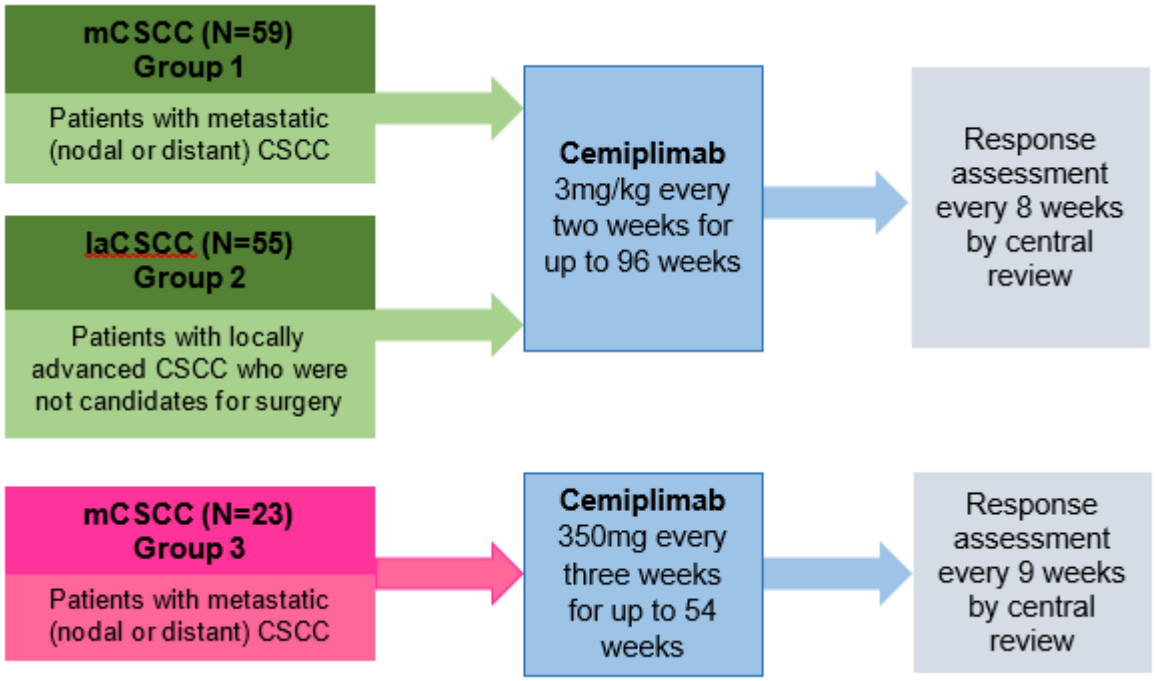
Key eligibility criteria included an ECOG performance status score of 0 or 1, adequate organ function and the presence of at least one lesion that could be measured according to RECIST version 1.1.[3] Patients were excluded if they had ongoing or recent (within 5 years) autoimmune disease that was treated with systemic immunosuppressive therapy, or if they had previously received treatment with anti-PD-1 or anti-PD-L1 therapy.[3]

The primary outcome for the study is ORR (defined as patients with complete response [CR] or partial response [PR]), according to independent central review. ORR was determined separately for Group 1 and Group 2.[45] Secondary endpoints included DoR, TTR, PFS, OS and safety. To account for the possibility of unconventional immune responses, patients could continue treatment beyond initial RECIST-defined progression informed by immune-related response criteria[48] and if the investigator believes this is in the best clinical interest of the patient. This is in line with other studies of immunotherapies indicating some patients treated with

immune-stimulating agents show disease progression, as defined by RECIST, before demonstrating subsequent clinical overall response and/or stable disease.

A study design schematic is presented in Figure 6.

Figure 6: Study design schematic, Phase II EMPOWER-CSCC 1



Key: CSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma.

A summary of methodology of both trials is presented in Table 4.

Table 4: Summary of methodology

Study Name	Phase I study	Phase II EMPOWER-CSCC 1
Location	47 sites in the US, Australia and Spain.	31 sites in the US, Australia and Germany.
Trial design	A Phase I, open-label, multicentre, first-in-human study.	Non-randomised, three-group, multicentre, multinational Phase II study.
Eligibility criteria for participants	Patients aged 18 years or older were eligible for the study if they met the following criteria: • Histologically or cytologically confirmed diagnosis of malignancy with demonstrated progression of a solid tumour with no alternative standard-of care. • For patients with laCSCC, acceptable reasons for surgery to be considered inappropriate included: – Recurrence of CSCC after two or more surgical procedures and an expectation that curative resection would be unlikely. – Substantial morbidity or deformity anticipated from surgery. • At least one measurable lesion as per RECIST v1.1. • ECOG PS ≤1 • Hepatic function: – Total bilirubin ≤1.5 X ULN – Transaminases ≤3 X ULN – ALP ≤2.5 X ULN • Serum creatinine ≤1.5 X ULN or estimated creatinine clearance >30mL/min. • Haemoglobin ≥9.0g/dL; absolute neutrophil count ≥1.5 x 10^9/L; platelet count ≥75 x 10^9/L	Patients aged 18 years or older were eligible for the study if they met the following criteria: • Histologically confirmed diagnosis of invasive CSCC. • At least one lesion measurable as per RECIST v1.1. • ECOG PS ≤1 • Hepatic function: – Total bilirubin ≤1.5 X ULN – Transaminases ≤3 X ULN – ALP ≤2.5 X ULN • Serum creatinine ≤1.5 X ULN or estimated creatinine clearance >30mL/min. • Haemoglobin ≥9.0g/dL; absolute neutrophil count ≥1.5 x 10^9/L; platelet count ≥75 x 10^9/L • Ability to provide signed informed consent and to comply with scheduled visits, treatment plans, laboratory tests and other study related procedures. • Anticipated life expectancy >12 weeks. In **Group 2 only**, the following eligibility criteria also applied: • Surgery deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon.

Study Name	Phase I study	Phase II EMPOWER-CSCC 1
	• Ability to provide signed informed consent and to comply with scheduled visits, treatment plans, laboratory tests and other study related procedures. Patients were excluded if they met any of the following criteria: • Ongoing or recent (within 5 years) evidence of significant autoimmune disease. • Prior treatment with an agent that blocks the PD-1/Pd-L1 pathway. • Prior treatment with other immune modulating agents that was within fewer than 4 weeks prior to the first dose of cemiplimab. • Untreated brain metastases considered active: – Patients with previously treated brain metastases were permitted to participate provided they were stable. • Immunosuppressive corticosteroid doses (>10mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab. • Active infection requiring therapy, including known HIV, HBV, HCV. • History of pneumonitis within the last 5 years • Any investigational or anti-tumour systemic treatment within 4 weeks prior to the initial administration of cemiplimab • History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatment in general, or to agents specifically used in the study. • Known allergy to doxycycline or tetracycline.	• Patients deemed not appropriate for radiation therapy, meeting at least one of the following criteria: – Previously received radiation therapy for CSCC, such that further radiation therapy would exceed the threshold of acceptable cumulative dose. – Judgement of radiation oncologist that such tumour was unlikely to response to therapy. – Radiation therapy was deemed to be contraindicated. • Consent to undergo biopsies of externally visible CSCC lesions when needed. • Natural history of the patient's disease would likely be life threatening within 3 years with currently available treatment options. Patients were excluded if they met any of the following criteria: • Ongoing or recent evidence of significant autoimmune disease. • Prior treatment with an agent that blocks the PD-1/Pd-L1 pathway. • Prior treatment with other immune modulating agents that was within 4 weeks prior to the first dose, associated with irAEs grade ≥1 or associated with toxicity that led to discontinuation. • Untreated brain metastases considered active. • Immunosuppressive corticosteroid doses. • Active infection requiring therapy, including known HIV, HBV, HCV. • History of pneumonitis within the last 5 years.

Study Name	Phase I study	Phase II EMPOWER-CSCC 1
	• Breastfeeding or positive pregnancy test; unwillingness to practice highly effective contraception. • History within the last 5 years of an invasive malignancy other than the one treated in this study and/or any leukaemia or lymphoma for at least 3 years prior to enrolment. • Acute of chronic psychiatric problems. • Patients with a history of solid organ transplant. Patients with prior corneal transplant could be allowed to enrol following discussion and approval from the medical monitor.	• Grade ≥3 hypercalcemia at the time of enrolment. • Any systemic anticancer treatment, investigational or standard of care within 30 days, radiation therapy within 14 days or planned to occur during the study period. • Documented allergic reaction or acute hypersensitivity reaction attributed to antibody treatment of cemiplimab. • Breastfeeding or positive pregnancy test; unwillingness to practice highly effective contraception. • Concurrent malignancy other than CSCC and/or history of malignancy other than CSCC within 3 years of date of first planned dose. • Acute or chronic psychiatric problems. • History of solid organ transplant. • Prior treatment with a BRAF inhibitory. • Any medical co-morbidity, physical examination findings or metabolic dysfunction. • Inability to undergo any contrast-enhanced radiologic response assessment. • Prior treatment with idelalisib.
Settings and locations where the data were collected	Central review for efficacy was performed by two independent radiologists and an adjudicator if needed.	Three independent central review committees were established to assess the primary variable by independent central review. An independent DMC was set up to provide independent oversight of safety, efficacy and study conduct. Data were collected locally by fully trained investigators. Site monitoring and pre-specified data

Study Name	Phase I study	Phase II EMPOWER-CSCC 1
		validation checks were regularly conducted to ensure data quality.
Trial drugs	Cemiplimab 3mg/kg q2w over 30 minutes IV, up to 48 weeks.	Groups 1 & 2: Cemiplimab 3mg/kg q2w over 30 minutes IV, up to 96 weeks. Group 3: Cemiplimab 350mg q3w, up to 54 weeks[a]
Permitted and disallowed concomitant medication	Any treatment administered from the time of informed consent until 30 days after the last study drug was considered as concomitant treatment. This included medications and other therapies for which administration started before the study and continued during the study, as well as any therapies started in the follow-up period (approximately 6 months) to treat a study drug related AE. All concomitant treatments were recorded in the study CRF with the generic name, dose, dose unit, frequency, indication and start/stop date as appropriate. Patients could not receive any standard or investigational agent for treatment of a tumour other than cemiplimab. Any other medication that was considered necessary for the patient's welfare could have been given at the discretion of the investigator. Physiologic replacement doses of systemic corticosteroids were permitted and a brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions was permitted. Treatment for bone metastases were permitted during the study.	Any treatment administered from the time of informed consent until 30 days after the last study drug was considered as concomitant treatment. This included medications and other therapies for which administration started before the study and continued during the study, as well as any therapies started in the follow-up period (approximately 6 months) to treat a study drug related AE. All concomitant treatments were recorded in the study CRF with the generic name, dose, dose unit, frequency, indication and start/stop date as appropriate. Patients could not receive any standard or investigational agent for treatment of a tumour other than cemiplimab. Any other medication that was considered necessary for the patient's welfare could have been given at the discretion of the investigator. Curative intent surgery was allowed for locally advanced patients with lesions considered unresectable at baseline but subsequently deemed resectable during the course of the study following discussion with the medical monitor.
Primary outcomes (including scoring methods and timings of assessments)	• Safety and tolerability, including TRAEs	• ORR, assessed by independent central review as per RECIST v1.1. ORR was determined by the proportion of patients with BORs of CR or PR in the FAS by group.

Study Name	Phase I study	Phase II EMPOWER-CSCC 1
Other outcomes used in the economic model/specified in the scope	• ORR, defined as the proportion of patients with a best overall response of CR or PR, per RECIST v1.1. • Disease control rate, defined as the proportion of patients with the best overall response of CR, PR and SD: – Duration of disease control, measured from the start of treatment until the first date of recurrent or progressive disease or mortality due to any cause. • DoR, defined as the time from the date of the first documented confirmed response (CR or PR) until the date of the first PD or mortality due to any cause, whichever occurred first: – Depth of response, defined as the percentage change or best percent change from baseline in sum of longest diameters of target lesions. • TTR, defined as the time from the start of treatment until first CR/PR. • PFS, measured from the start of treatment until the first date of recurrent or progressive disease (radiographic) or mortality due to any cause. • OS, measured from the start of treatment to mortality due to any cause.	• ORR based on investigator review, as per RECIST v1.1. • DoR, measured from the time of CR or PR (whichever was first recorded) until the first data of PD (radiographic), or mortality due to any cause. • TTR, determined by independent central review and by investigator assessment. • PFS, measured from the start of treatment until the first date of PD (radiographic) or mortality due to any cause. • OS, measure from the start of treatment until death due to any cause. • Safety, including AEs, irAEs and SAEs.
Pre-planned subgroups	N/A	Subgroup efficacy analysis were performed based on the following factors: • Gender (male, female) • Age group (<65, ≥65) • Race (white, non-white)

Study Name	Phase I study	Phase II EMPOWER-CSCC 1
		• Geographic region (North America, Europe and rest of the world) • Number of prior systemic therapies. • ECOG (0, 1) • Prior systemic anticancer therapy (yes or no) • Metastatic status (distant or nodal only; for **Group 1 only**)

Key: AE, adverse event; ALP, alkaline phosphatase; BOR, best overall response; CR, complete response; CRF, case report form; CSCC, cutaneous squamous cell carcinoma; DMC, data monitoring committee; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; irAE, immune-related adverse events; IV, intravenous; laCSCC, locally advanced cutaneous squamous cell carcinoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria In Solid Tumors; SAE, serious adverse events; SD, stable disease; TRAE, treatment-related adverse event; TTR, time to response; ULN, upper limit of normal.
Notes: [a], Data for this cohort are not yet available and are therefore not considered in efficacy analyses.
Source: Migden *et al*. 2018[3]; Phase II EMPOWER-CSCC 1 CSR, 2018[45]; Phase I study CSR, 2018.[46]

B.2.3.1.3. Integrated analysis

As discussed in Section B.2.1, in order to provide the most robust and precise assessment of efficacy data from the Phase II EMPOWER-CSCC 1 and the Phase I study was pooled. This, integrated analysis, formed the basis of the regulatory submission and allowed for greater precision in the efficacy of cemiplimab. Pooling of the two studies was clinically plausible due to the similar study methodologies and eligibility criteria of patients. Clinical expert opinion was sought, further confirming pooling of the Phase I and Phase II data was suitable.

In addition, data for the mCSCC and laCSCC populations were also pooled to provide one integrated population comprising both subgroups of patients.Clinical expert opinion confirmed pooling of the two populations was appropriate as these are advanced, high risk patients at the last stages of disease who would be treated in a similar manner. Clinical experts did note that, as a proportion of laCSCC patients are still potentially curable, these patients could be viewed as different to mCSCC patients; contraindication to surgery and curative radiation was a key inclusion criterion in both studies and therefore any laCSCC patients who were potentially curable would have been excluded from the trials. Finally, available comparator data are limited to populations including both laCSCC and mCSCC patients, thus the integrated analysis comprising both mCSCC and laCSCC patients, is presented, shaping the basis for the cost-effectiveness analysis.

To achieve the integrated efficacy analyses, two issues were addressed. Firstly, in the original analysis of the Phase I study, the definition of mCSCC required the presence of distant metastases. Patients whose extent of disease was regional nodal metastases only were not considered to have mCSCC and were instead enrolled into the laCSCC cohort. Conversely, in the Phase II EMPOWER-CSCC 1 study, mCSCC was defined as distant metastases and/or regional nodal involvement. For the integrated analysis, the definitions of mCSCC and laCSCC used in the Phase II EMPOWER-CSCC 1 study are used meaning patients in the Phase I study who had nodal involvement have been reassigned so they now would qualify as mCSCC.

Secondly, in the Phase II EMPOWER-CSCC 1 study, the efficacy data from laCSCC is limited to those patients with potential for sufficient follow-up, defined as having

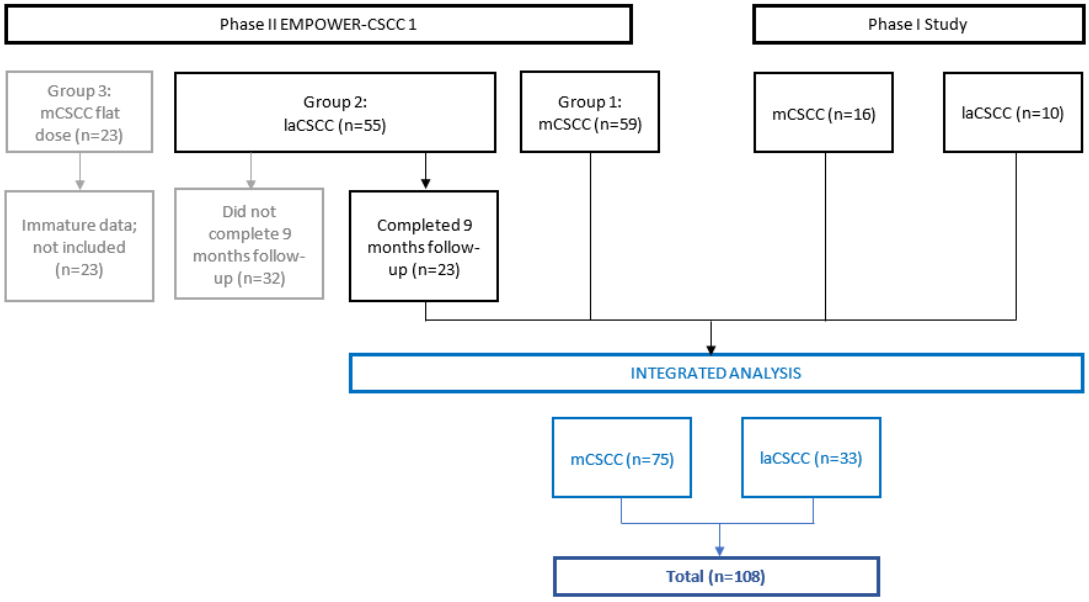
the potential for 9 months of follow-up. A 9-month of follow up was chosen in order to ensure that the minimum requirement for duration of response of 6 months, as set by the US Food and Drug Administration (FDA), was met. As such, the integrated analysis consisted of:

- A pooled analysis of 75 mCSCC patients across the two studies. This analysis includes 59 patients from the Phase II EMPOWER-CSCC 1 study and 16 from the Phase I study.
- A pooled analysis of 33 laCSCC patients across the two studies. This analysis includes 23 patients from the pre-specified interim analysis of the Phase II EMPOWER-CSCC 1 study and 10 patients from the Phase I study.

The full analysis set (FAS) included 108 patients. Patients with mCSCC who received a flat dose of 350mg cemiplimab in the Phase II EMPOWER-CSCC 1 study (Group 3) were not included in the integrated analysis. Enrolment to this group was opened after completion of enrolment to the initial mCSCC cohort therefore data for this cohort are currently unavailable.

A flow diagram summarising the integrated analysis is presented in Figure 7.

Figure 7: Summary of integrated analysis across Phase I and II



Key: laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma.

B.2.3.2. Baseline characteristics

Baseline characteristics for the integrated analysis alongside each study are presented in Table 5. Baseline characteristics of the mCSCC and laCSCC populations are presented in Appendix L.

B.2.3.2.1. Phase I study

In the Phase I study, the advanced CSCC population consisted predominantly of older white males. The median age of patients was 73 years (range: 55–88). With response to previous treatment for CSCC, 15 patients (58%) had previously received systemic therapy and 20 (77%) had received RT.

B.2.3.2.2. Phase II EMPOWER-CSCC 1

Overall, baseline demographics were similar in all groups with most patients white ([redacted]), male ([redacted]) and aged 65 years or older ([redacted]).[45] Of note, the age of this population is likely to be younger than seen in clinical practice with clinicians estimating the average UK patient age to be towards the upper end of the range included in the trials. Further discussion on generalisability of the trial is presented in Section B.2.13.

In Group 1, [redacted] of the patients received prior cancer related systemic therapy ([redacted]) compared to Group 2, where [redacted] had received prior therapy ([redacted]) (further discussed in Section B.2.10).[45] A majority of patients ([redacted]) had prior cancer related surgery with the median number of cancer related surgeries being [redacted] (range: [redacted]) and 72% of patients had prior cancer related RT.

Table 5: Baseline characteristics, integrated analysis, total population

	Integrated analysis (n=108)	Phase I study (n=26)	Phase II EMPOWER-CSCC 1 (N=137)
Male, n (%)	[redacted]	21 (80.8)	[redacted]
Median age (range)	[redacted]	72.5 (52 [redacted] 88)	[redacted]
Weight, mean kg (SD)	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)	[redacted]	0: 10 (38.5) 1: 16 (61.5)	[redacted]

	Integrated analysis (n=108)	Phase I study (n=26)	Phase II EMPOWER-CSCC 1 (N=137)
Prior cancer related systemic therapy, n (%)	[redacted]	15 (57.7)	55 (40.1)
No. of regimens at baseline, n (%) 0 1 ≥2	[redacted]	[redacted]	[redacted]
Prior cancer related surgery, n (%)	[redacted]	24 (92.3)	126 (92.0)
Prior cancer related RT, n (%)	[redacted]	[redacted]	[redacted]

Key: ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; ITT, intent-to-treat; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; PS, performance status.
Source: Migden *et al*. 2018[3]; Owonikoko *et al.* 2018[49]; Phase II EMPOWER-CSCC 1 CSR, 2018[45]; Sanofi data on file, 2018[41]; Phase I study CSR, 2018.[46]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The hypotheses and associated statistical analysis methods are presented in Table 6.

The primary efficacy analysis for both mCSCC and laCSCC patients who are not candidates for surgery, is based on an integrated analysis of the Phase I and Phase II EMPOWER-CSCC 1 studies. Integration of the data was deemed both straightforward and acceptable by the EMA, due to the similarities between the study designs and patient populations.[41] As already noted, the definitions of mCSCC and laCSCC differed between the two studies and so patients in the Phase I study were recategorised.[47]

By integrating results from the two studies, the data set represents the largest prospective clinical investigation of any systemic therapy for patients with mCSCC or laCSCC.[41] Furthermore, the integrated results increase the precision of the confidence intervals (CIs) for the primary endpoint of ORR compared to the individual studies, with the longer follow-up of the Phase I study able to increase the

power of the data. This was accepted by both UK clinicians and the EMA, as previously discussed.[41] Efficacy analyses were conducted on the FAS, which included 108 patients as described previously. Of note, all integrated analyses are descriptive and no hypothesis testing was conducted based on integrated data.[41] Safety analyses were conducted on the safety analysis set, which included all advanced CSCC patients who received at least 1 dose of cemiplimab monotherapy in either study, on or before the data cut-off date defined for each study. The safety analysis set therefore also includes patients in the Phase II EMPOWER-CSCC 1 who received a 350mg flat dose of cemiplimab (n=23 patients).

Integrated results presented within this submission are based on a median duration of follow-up of 8.56 months (range: 0.8–15.9 months) for the total advanced CSCC population.[47] Results for the mCSCC and laCSCC populations are separately presented in Appendix L.

The number of patients randomised to treatment arms is provided in Appendix D.2, alongside a Consolidated Standards of Reporting Trials (CONSORT) diagram of participant flow.

Table 6: Summary of statistical analyses

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Phase I study	To evaluate the safety and tolerability of cemiplimab monotherapy.	For continuous variables, descriptive statistics included the number of patients reflected in the n, mean, median, SD, minimum and maximum. In addition, the 25^{th} and 75^{th} percentiles are included. For categorical or ordinal data, frequencies and percentages are displayed for each category. For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its 95% CIs were summarised by the KM method. ORR, DCR was summarised using the Clopper-Pearson method.	Sample sizes for each of the 26 expansion cohorts were determined separately. For the CSCC cohort, 10 patients with mCSCC and 20 patients with laCSCC, were to be enrolled.	If a patient had progressed or died at the data cut-off date, DoR was to be censored at the time of the last adequate tumour assessment before the cut-off date. Patients who never progressed while being followed for duration of DCR will be censored at the last valid tumour assessment. If a patient had not progressed or died at the date of the analysis cut-off, PFS was to be censored at the time of the last adequate tumour assessment before the cut-off date. If a patient had no post-baseline evaluation, PFS was to be censored at the treatment start date. If a patient was not known to have died at the date of the analysis cut-off, OS was to be censored at the last date that patient was documented to be alive.

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Phase II EMPOWER-CSCC 1	For Group 1, the null hypothesis was an ORR of 15%. For Group 2, the null hypothesis was an ORR of 25%.	For continuous variables, descriptive statistics included the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum and maximum. In addition, 25th and 75th percentiles were provided. For categorical or ordinal data, frequencies and percentages were displayed for each category. The denominator was the analysis population used for the summary measure. For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its 95% CIs were summarised by the KM method. Statistical analysis for efficacy was conducted independently for each group. For regions where alpha spending was required, 2-sided alpha of 0.0001 was allocated for interim analysis and two-sided alpha of 0.0499 will be preserved for the final analysis. Two-sided 95% exact binomial CIs were derived using the Clopper-Pearson method.	For Group 1, 50 patients were required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a two-sided significance level of no more than 5% if the true ORR was 34%. For Group 2, 72 patients were required to provide at least 90% power to reject a null hypothesis of an ORR of 25% at a two-sided significance level of no more than 5% if the true OR was 44%. Sample sizes were increased by 5% to account for patients who might withdraw prematurely from the study. Hence the sample sizes were 53 patients for Group 1 and 76 for Group 2, a total of 129 patients.	A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, coding, correcting, and releasing) was maintained and stored with the manufacturer. Unless otherwise stated there were no imputations for missing data. Disease progression was censored at the date of baseline tumour assessment + 1 day. DoR and PFS was censored at the last tumour assessment date for patients without disease progression.

Key: CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; CSR, clinical study report; DCR, disease control rate; DoR, duration of response; KM, Kaplan–Meier; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, stable disease.
Source: Phase I study CSR, 2018[46]; Phase II EMPOWER-CSCC 1 CSR, 2018.[45]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

A summary of quality assessment for both studies is presented in Appendix D.3.

Both studies were conducted in accordance with Good Clinical Practice (GCP) guidelines by qualified investigators using a single protocol to promote consistency across sites and measures taken to minimise bias. While CSCC is common, advanced CSCC occurs in a very small subset estimated to be ~4%. With such a low incidence of advanced CSCC, recruitment to a comparative study could take several years. In addition, currently there are no licensed therapies available for patients with advanced CSCC and treatment patterns are variable hence identifying appropriate comparators to be included in a trial is a challenge. Current treatments used have suboptimal and nondurable outcomes with survival less than a year. With early evidence of significant efficacy in a phase I trial of cemiplimab, and advice from regulators to submit early data for approval, it would not only be unethical to conduct a comparative study with less effective therapy as a comparator, but such a study would also violate the principles of clinical/ therapeutic equipoise.

Therefore, data is taken only from single-arm Phase I and II studies; comparative efficacy has been made through an ITC as presented in Section B.2.8. Although both trials were designed as open-label, the primary endpoint of ORR for the phase II study is not subjectively assessed and was analysed by independent central review; therefore, outcome assessors were blinded. The most common reason for withdrawal in both studies was disease progression, accounted for within the efficacy assessments. Patient withdrawals for reasons other than disease progression were accounted for with standard censoring methods.

Disease evaluation and safety evaluation methods are consistent with other studies of NMSC[50-53] and outcomes assessments were all conducted in accordance with trial validated methodology. However, in recognition of the limitations of validated RECIST criteria for assessing immunotherapy drugs (see Section B.2.13), patients were allowed to receive treatment beyond RECIST-defined progression in both studies to better reflect clinical practice. Despite the lack of UK-sites in either trial, both trials are thought to be generally reflective of routine clinical practice in England

although patients in the trials are likely younger and fitter than the UK population of interest, as can be expected in clinical trials. Patients with advanced CSCC were eligible for inclusion in the study, the population of direct relevance to the decision problem. It is also important to note that alongside clinical efficacy and safety outcomes, HRQL outcomes were also measured (presented in Section B.2.6.4), as requested by reimbursement agencies.

The feasibility and justification for pooling of the studies has been discussed previously.

B.2.6. Clinical effectiveness results of the relevant trials

Within this section, results for the integrated analysis are presented along single study data within tables, but all figures and text focus on the integrated analysis. Results for single study data are presented in Appendix L.

B.2.6.1. Overall response rate (primary outcome)

Treatment with cemiplimab demonstrates substantial and durable tumour response, with an ORR of [redacted]% (95% confidence interval [CI]: [redacted]) seen in all patients with advanced CSCC by independent central review, presented in Table 7.[41] Importantly, [redacted]% of advanced CSCC patients showed a benefit while receiving treatment, reporting either a CR ([redacted]%), PR ([redacted]%) or SD ([redacted]%). The high response rate seen with cemiplimab is one of the highest observed in solid tumours across the whole PD-1/PD-L1 inhibitor landscape.[23] The number of patients achieving a complete response may be lower than expected due to the definition of complete response in the locally advanced patient population (group 2) in the phase II trial. This included both World Health Organization and RECIST 1.1 as appropriate, which some clinical experts have suggested can be challenging to satisfy due to residual scarring at the site of a lesion even after resolution. In addition, in patients believed to achieve a CR based on clinical response criteria, a stringent confirmation was employed in the trial, in discussion with EMA, using tumour biopsies to distinguish CR versus PR.

Table 7: Overall response rate, independent central review, FAS population

	Integrated analysis (N=108)	Phase I Study (N=26)	Phase II EMPOWER-CSCC 1 (N=82)
Best overall response, n (%)			
CR (%)	[redacted]	0	[redacted]
PR (%)	[redacted]	13 (50.0)	[redacted]
SD (%)	[redacted]	[redacted]	[redacted]
Non-CR/Non-PD (%)	[redacted]	[redacted]	[redacted]
PD (%)	[redacted]	[redacted]	[redacted]
NE* (%)	[redacted]	3 (11.5)	[redacted]
ORR, n (%) [95% CI]	[redacted]	13 (50.0) [29.9, 70.1]	[redacted]
DCR[a], n (%) [95% CI]	[redacted]	20 (76.9) [56.4, 91.0]	[redacted]
Durable DCR, n (%) [95% CI]	[redacted]	17 (65.4) [44.3, 82.8]	[redacted]
Mean TTR, months (SD)	[redacted]	[redacted]	[redacted]
<2 months	[redacted]	[redacted]	[redacted]
2 to 4 months	[redacted]	[redacted]	[redacted]
4 to 6 months	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; CSCC, cutaneous squamous cell carcinoma; DCR, disease control rate; FAS, full analysis set; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.
Notes: [a], CR+PR+SD+Non-CR+Non-PD. *Patients without a post baseline assessment were categorized as not evaluable (NE)
Source: Sanofi Data on File, 2018[41]; Owonikoko *et al.* 2018.[49]

Results for individual mCSCC and laCSCC populations are presented separately in Appendix L. Cemiplimab demonstrated consistent response in terms of the primary end point (ORR) across studies in both laCSCC and mCSCC. An ORR of at least [redacted]% was achieved in both populations across both studies with an ORR of [redacted] in the integrated analysis as presented in Figure 8.

Figure 8: Subgroup analysis of ORR

Key: CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; ORR, overall response rate.
Notes: Study 1423 related to the Phase I study. Study 1540 relates to the Phase II EMPOWER-CSCC 1 study. Combined CSCC relates to the integrated analysis.
Source: Sanofi data on file.

In the integrated analysis, median DoR [redacted], as presented in Table 8, with responses ranging from [redacted] ("+" denotes ongoing at last assessment).[41] At the data cut-off, [redacted]% of responders with advanced CSCC had an observed DoR ≥6 months. In addition, among the [redacted] responding patients, [redacted]% were still in response at the time of last disease assessment, further demonstrating the potential for durable, clinically meaningful responses to cemiplimab. Durability of response is visually demonstrated in a patient case study from the Phase II EMPOWER-CSCC 1 study as shown in Figure 9. This reveals the visually significant improvement in disease from screening to Week 32.

Figure 9: Durable response seen with cemiplimab in an 85-year-old male patient from baseline (left) to week 32 (right)

Note: Photo from Phase II EMPOWER-CSCC 1 study shows an 85-year-old man with a supraclavicular lesion before (left) and after treatment (right).
Source: Migden *et al*. 2018.[3]

Finally, in responding patients, maximal or near-maximal depths of responses in target lesions were usually evident at the first response assessment at Week 8 and responses usually persisted. This means that for responding patients the measurable tumour had disappeared or nearly disappeared. Among the [redacted] patients with confirmed CR or PR, the overall median TTR was [redacted]).[41] The speed of response in tumour shrinkage for a patient is demonstrated in Figure 10 showing the significant visual difference after just 6 weeks of treatment with cemiplimab.

Figure 10: Visual response seen with cemiplimab in a 62-year-old male patient, from baseline (left) and after 6 weeks (right))

Note: Photo from phase I study shows a 62-year-old male with multiple scale CSCC lesions before (left) and after treatment (right).
Source: Migden *et al.* 2018.[3]

Table 8: Duration of response, FAS population

	Integrated analysis (N=108)	Phase I Study (N=13)	Phase II EMPOWER-CSCC 1 (N=38)
KM estimated DoR			
Events, n (%)			
Median months (95% CI)		NR (NE, NE)	
Observed DOR, n (%)			
N (min, max)			
≥4 months			
≥6 months			
≥8 months			
≥12 months			

Key: CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; DoR, duration of response; FAS, full analysis set; KM, Kaplan–Meier; NE, not evaluable; NR, not reported.
Source: Sanofi Data on File, 2018[41]; Owonikoko *et al.* 2018.[49]

By investigator assessment, ORR was % and the observed range of responses was , demonstrating a high degree of concordance between the two assessment methods.[41]

B.2.6.2. Overall survival (secondary endpoint)

Median OS [redacted] for the advanced CSCC patient population, as presented in Figure 11.[41] This demonstrates that at the time of data cut off [redacted] The estimated 12-month event-free rate is [redacted]% (95% CI: [redacted]).

Table 9: Overall survival, FAS population

	Integrated analysis (N=108)	Phase I Study (N=26)	Phase II EMPOWER-CSCC 1 (N=82)
Median OS, months (95% CI)	[redacted]	NR ([redacted])	[redacted]
Estimated event-free probability, % (95% CI)			
4 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
8 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
16 months	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; FAS, full analysis set; NE, not evaluable; OS, overall survival.
Source: Sanofi Data on File, 2018[41]; Papadopoulos *et al.* 2018.[54]

Figure 11: Kaplan–Meier plot of overall survival, integrated analysis, FAS population

Key: CSCC, cutaneous squamous cell carcinoma; FAS, full analysis set.
Source: Sanofi Data on File, 2018.[41]

B.2.6.3. Progression-free survival (secondary endpoint)

Median PFS by independent central review [redacted] for the advanced CSCC patient population, as presented in Figure 12.[41] The estimated 12-month event-free rate is [redacted]% (95% CI: [redacted]), presented in Table 10.

Table 10: Progression-free survival, FAS population

	Integrated analysis (N=108)	Phase I Study (N=26)	Phase II EMPOWER-CSCC 1 (N=82)
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]
Estimated event-free probability, % (95% CI)			
4 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
8 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
16 months	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; FAS, full analysis set; NE, not evaluable; PFS, progression-free survival.
Source: Sanofi Data on File, 2018[41]; Papdopoulos *et al.* 2018.[54]

Figure 12: Kaplan–Meier plot of progression-free survival, integrated analysis, FAS population

Key: CSCC, cutaneous squamous cell carcinoma; FAS, full analysis set.
Source: Sanofi Data on File, 2018.[41]

B.2.6.4. Health-related quality of life (secondary endpoint)

B.2.6.4.1. Phase II EMPOWER-CSCC 1

Currently there is only limited data available from the phase II trial with European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core-30 question (QLQ-C30) scores [redacted] Figure 13 [redacted], as presented in Figure 14.[45] This reduction may be considered clinically meaningful.[43] As the data matures the impact of Cemiplimab on QoL is likely to become clearer.

Figure 13: EORTC QLQ-C30 global health status, Phase II EMPOWER-CSCC 1 study, FAS population

Key: CSCC, cutaneous squamous cell carcinoma; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire core-30; FAS, full analysis set; SE, standard error.
Source: Phase II EMPOWER-CSCC 1 CSR, 2018.[45]

Figure 14: EORTC QLQ-C30 pain subscale, Phase II EMPOWER-CSCC 1 study, FAS population

Key: CSCC, cutaneous squamous cell carcinoma; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire core-30; FAS, full analysis set; SE, standard error.
Source: Phase II EMPOWER-CSCC 1 CSR, 2018.[45]

Clinicians noted that there is no validated specific QoL questionnaire for advance CSCC. However, the lesions and scarring associated with CSCC can be extremely disfiguring; typically, they are in UV-exposed areas and therefore areas visible in public. Other visibly disfiguring conditions, such as facial psoriasis, have been shown to have a large, negative impact on HRQL.[55, 56] The sense of stigma associated with such conditions may be the contributing factor resulting in reduced HRQL[56]; indeed, facial psoriasis clearance was associated with improved HRQL.[55] As such, CSCC is likely to affect patients' psychological state and general QoL. At a UK advisory board, clinical experts agreed that although the EORTC QLQ-C30 is generally suitable for capturing QoL data, it may not be as sensitive in capturing the anxiety and depression experienced by patients with advanced CSCC. They also stated that the visible differences seen after treatment with cemiplimab (Figure 9 and Figure 10) can reasonably be expected to have a positive impact on QoL with the potential to reduce burden of disease for the patient.

B.2.7. Subgroup analysis

Exploratory subgroup analysis in the advanced CSCC population showed efficacy across all demographic and baseline disease characteristics subgroup.[41]

B.2.7.1. Overall response rate

[redacted] The ORR was [redacted] for advanced CSCC patients who had not received prior cancer related systemic therapy ([redacted]) than for patients who had received prior cancer related systemic therapy [redacted] In the 108 patients evaluable for efficacy, the ORR in patients 65 years or older was [redacted]% and in patients 75 years or older [redacted]%.

Subgroup analysis of OS and PFS in the integrated analyses, as well as subgroup analysis for the mCSCC and laCSCC populations separately, are presented in Appendix E.

B.2.8. Meta-analysis

No meta-analysis was performed.

B.2.9. Indirect and mixed treatment comparisons

No studies were identified through the SLR (described in Appendix D.1) that investigated cemiplimab in comparison to chemotherapy or BSC for the treatment of advanced CSCC.

In the absence of head to head data, individual patient level data (IPD) from the two cemiplimab trials was used to perform a naïve comparison and an unanchored population adjusted indirect comparison of cemiplimab versus the available literature for platinum-based chemotherapy, for OS, PFS and ORR.

B.2.9.1. Methods

Overall, a total of 57 citations evaluating 56 studies were included in the SLR (described in Appendix D.1). The studies included six single-arm clinical trials, five prospective observational studies, three non-randomised multi-cohort trials, one cross-sectional survey and 41 retrospective observational studies but no RCTs. One additional single-arm trial was identified after the review had been conducted and included in the feasibility assessment, resulting in a total of 57 included studies.

A large amount of heterogeneity was observed amongst the final list of included studies, mostly due to differences in studies' eligibility criteria and featured interventions. A total of 39 studies only recruited patients with regional mCSCC, all of which featured surgical interventions with or without RT. After reviewing the number of patients with regional mCSCC in the Phase II EMPOWER-CSCC 1 study expected to be eligible for lymph node resection, it was concluded that no comparisons with the identified surgery studies were likely to be feasible. From the remaining 18 studies, the feasibility assessment sought to determine which featured interventions likely to be used in clinical practice, contained a population in line with the target population from the cemiplimab trials and also reported the necessary outcomes information to conduct a population adjusted comparison. Full details of the feasibility assessment are presented in Appendix D.1.3.1. A total of five studies were found to meet these criteria; in addition to the two cemiplimab studies, these seven studies formed the basis of the comparison.

Key differences between the studies related to study design (that is prospective single-arm trials versus retrospective database analysis) and treatment definitions (weight-based versus flat dosing of cemiplimab and unknown distribution of platinum treatments). Differences were also identified in terms of age, gender, disease stage, tumour grade, ECOG status, prior treatments and tumour site. This is further discussed in Appendix D.1.3.2.

Of note, the SLR and subsequent ITC were conducted from a global perspective and as such included a number of comparators not of direct relevance to the UK setting. In particular, this SLR identified evidence for a number of epidermal growth factor receptor (EGFR) inhibitors (for example cetuximab, gefitinib and erlotinib). However, these treatments are not licenced in the UK for this indication and therefore Sanofi would not consider them as a standard of care for the purposes of this appraisal (this evidence is further discussed in section B.3.2.3). Instead, results presented in this submission will focus on comparisons of interventions of relevance to the UK setting, namely cemiplimab, chemotherapy and BSC. No studies were identified that investigated BSC and, as such, only studies comparing cemiplimab to chemotherapy are presented. This has been validated by UK clinicians who stressed that this comparison would provide a conservative estimate of cemiplimab efficacy.

Therefore, the studies of interest are the two prospective clinical trials of cemiplimab, discussed in Section B.2.3, and one retrospective chart review of platinum-based chemotherapy by Jarkowski and colleagues, described in detail in Appendix D.1.3.4.[6] Full results are presented in Appendix D.1.3.4.

Due to the lack of RCTs identified in the SLR, a standard network meta-analysis (NMA) of RCTs is not feasible. Therefore, individual patient level data (IPD) from the two cemiplimab trials was used to perform a naïve comparison and an unanchored population adjusted indirect comparison of cemiplimab versus platinum-based chemotherapy, in terms of OS, PFS and ORR. As per the clinical and safety data presented within the submission, and due to the similarities between Phase II EMPOWER-CSCC 1 and the Phase I study, these trials were pooled with all patients from both trials included in the base case. In the Jarkowski study, only patients who received platinum-based chemotherapy were included.

B.2.9.1.1. Prognostic factors

When conducting indirect comparisons on the basis of non-randomised studies, there will always be uncertainty regarding unknown or unmeasured prognostic factors that may influence the outcome of interest but are not captured in the model. 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. 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.

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.

Results

Forest plots of OS hazard ratios (HRs), PFS HRs, and response odds ratios (ORs) for subgroups of identified prognostic elements based on the pooled IPD from the cemiplimab trials are presented in Figures 4, 5 and 6 of Appendix D.1.3.3. Results were generally consistent with what was observed in the published literature. As expected, OS and PFS results were both significantly more favourable in patients with ECOG score of 0 compared to those with scores of 1 or above. In addition, patients without prior experience of systemic therapies compared to those with such experience, and patients with lesions in the trunk or extremities compared with those with head and neck lesions had significantly better OS and PFS results, respectively. The latter subgroup also had a significantly higher ORR. These results are in line with existing data that shows lesions of the trunk or extremities usually do not present with metastases and therefore exhibit less aggressive biological behaviour.[57]

B.2.9.2. Analysis

In cases where a standard NMA of RCTs is not feasible, IPD from an index trial, such as the phase I and the phase II, EMPOWER-CSCC 1 trials, can be used to perform an unanchored population-adjusted indirect comparison.[58] Two main types of analyses are described by NICE: outcomes regression based indirect comparisons (also known as a simulated treatment comparison [STC]) and matching adjusted indirect comparisons (MAICs). The validity of either approach is largely dependent upon how well the estimated models describe the outcome of interest.

B.2.9.2.1. Simulated treatment comparison

The STC involved creating a regression model for cemiplimab and modelling the outcome of interest as a function of relevant patient related factors using pooled IPD from the cemiplimab studies. This regression model was then used to predict the outcomes for cemiplimab that would be observed in single-arm studies of relevant comparators for which only aggregate study level data were available.

Cox model for time-to-event outcomes

The regression model for time-to-event outcomes as a function of relevant covariates using IPD was developed using the Cox proportional hazards framework:

$$\ln(h_{it}) = \beta_{0t} + \sum_{c=1}^{C} \beta_c^x (x_{ci})$$

Where (h_{it}) reflects the underlying hazard rate at time point *t* for subject *i*, β_{0t} is the baseline log-hazard at time *t*, x_{ci} is the value of covariate *c* for subject *i* and β_c^x reflects the impact of covariate *c* on the log hazard. The Cox model is semi-parametric because it is assumed that the baseline hazard follows a particular survival function, whereas the covariates enter the model in a linear fashion. A defining feature of the Cox model is that the hazard with treatment over time is modelled multiplicatively relative to the baseline hazard over time.

The modelling of the log hazards can be conducted on centred covariate, thus reframing Equation 1 as:

$$\ln(h_{it}) = \beta_{0t} + \sum_{c=1}^{C} \beta_c^x (x_{ci} - \bar{x}_c)$$

Where β_{0t} is now the baseline hazard at the average of the covariate values in the IPD set. This Cox model can be used to predict the hazard over time given a certain set of values for the covariates included in the model, despite the absence of a particular survival distribution for the baseline hazard over time. More specifically, the observed baseline hazard in the index trial can be used as the reference to predict the hazard over time for another population with different covariate values,

based on the covariate estimates for β_c^x. Bootstrap samples were used to estimate the standard errors of the predicted treatment effect.

Logistic model for dichotomous outcomes

For dichotomous outcomes, a logistic regression model was used to describe the probability of the outcomes of interest as a function of the covariates:

$$\text{logit}(p_i) = \beta_0 + \sum_{c=1}^{\text{C}} \beta_c^x (x_{ci})$$

Where p_i is the probability of the outcome of interest for individual *i*, β_0 represents the log odds corresponding to a defined reference category and β_c^x is the coefficient of covariate x_{ci}.

B.2.9.2.2. Matching-adjusted indirect comparison models

A logistic propensity score model was used to estimate weights for the IPD from the index trial so the weighted mean baseline characteristics match those observed for a target population. The propensity score is defined as the probability of treatment assignment conditional on baseline covariates. This is determined via logistic regression, based on the IPD from the index trial:

$$\text{logit}(\text{T}) = \beta_0 + \sum_{i=1}^{C} X_i$$

Where T represents the treatment group and X_i are the *i=1…C* covariates under consideration. In cases where the algorithm used to estimate the weights did not converge, variables were removed in stepwise fashion in a pre-determined order until convergence is achieved. Outcomes for the index treatment were then predicted for the target population by reweighting the observed outcomes from the index trial.

Specifically, mean outcomes for each target population were then estimated by taking a weighted average of the outcomes of individuals in the index trial. The weighting is defined as:

$$\widehat{Y_{(T)}} = \frac{\sum_{i=1}^{N} Y_{i(I)} w_i}{\sum_{i=1}^{N} w_i}$$

Where $\widehat{Y_{(T)}}$ is the estimated mean outcome in the target population, $Y_{i(I)}$ is the observed outcome for individual *i* in the index population, w_i is the weight for individual *i* and *N* is the number of individuals in the index trial. When the weights are estimated with a propensity score logistic regression model, they represent the odds of being enrolled in the target trial versus the index trial.

The validity MAIC model depends on the overlap between the IPD and the aggregate population. When there is little overlap between populations, the estimates become heavily influenced by relatively few individuals. A measure of the validity of the model the effective sample size (ESS):

$$\mathrm{ESS} = \frac{\left(\sum_{t=1}^{T}\sum_{i=1}^{N} w_{it}\right)^2}{\sum_{t=1}^{T}\sum_{i=1}^{N} w_{it}^2}$$

This is an adjustment of the sample size that accounts for the weighting of the observations and the resulting correlations between estimated responses. As with the typical sample size, a large value is preferable to a small value, as the larger sample contains more information.

For OS and PFS, a HR was calculated using a Cox regression incorporating the weights produced and new effective sample size after matching the cemiplimab data to each of the external trial populations. For response, an odds ratio was calculated using Fisher's test on a weighted 2 x 2 contingency table, again incorporating the weights and new effective sample size.

B.2.9.2.3. Selection of covariates

Covariates included in the core model for the analysis were those reported as statistically significant in at least one study identified in the targeted literature review of prognostic factors. Of these, only age, disease stage, tumour site and tumour grade were reported in the comparator studies and therefore could be adjusted for in the analyses.

The fit of the two alternative models, along with other permutations, were compared using the Akaike information criterion (AIC). The AIC of the different models that

were fitted to the pooled IPD from the cemiplimab trials are presented in Table 10 of Appendix D.1.3.5. The extended model appeared to provide a better fit to the data when compared with the core model. However, after removing gender from the extended model the two became comparable across all outcomes. The extended models also resulted in coefficients which were in a direction contrary to what was expected based on the evidence base for prognostic factors which can again be traced to the small number of patients and events within certain strata. The core model was therefore selected for analysis as it represented the best combination of overall fit and plausibility.

B.2.9.2.4. Published Kaplan–Meier curves and software

For each treatment arm of each study in the analyses for which only published data was available, the reported Kaplan–Meier (KM) curves were digitised. The algorithm proposed by Guyot *et al*., 2011 was applied to simulate IPD for each treatment arm and then used as the basis for each pairwise comparison.[59]

Estimation of the trial specific outcomes of interest with the index intervention for each single-arm trial were performed in R using the 'Survival' and 'pec' packages.

B.2.9.3. Results

B.2.9.3.1. Overall survival

The unadjusted and population adjusted KM curves for cemiplimab, as well as the observed data from the Jarkowski 2016 study, are presented in Figure 15. Parameters from the STC, as well as baseline characteristics pre/post matching and the effective sample size from the MAIC, are presented in Table 11 of Appendix D.1.3.5. Both population adjustment methods led to upward shifts in the cemiplimab curve leading to improved survival estimates for cemiplimab. In the MAIC, the majority of this shift was due to six patients who received disproportionately higher weights than the rest of the sample with the effective sample size also being reduced by 65.7% to 37. [redacted]

[redacted] Figure 16 [redacted] (with statistical significance reached with the MAIC method).

Figure 15: Unadjusted and population adjusted Kaplan–Meier curves for OS

Key: MAIC, matching-adjusted indirect comparison; O-R, outcomes regression; OS, overall survival.

Figure 16: Forest plot of hazard ratios of OS for cemiplimab versus chemotherapy

Key: CI, confidence interval; MAIC, matching-adjusted indirect comparison; OS, overall survival.
Note: naïve refers to the unadjusted indirect comparison

B.2.9.3.2. Progression-free survival

The unadjusted and population adjusted KM curves for cemiplimab, as well as the observed data from the Jarkowski 2016 study, are presented in Figure 17 with

parameters from the STC presented in Table 12 of Appendix D.1.3.5. A similar pattern was observed as in the PFS comparison, where the MAIC led to a bigger upward shift in the curve (improved PFS) due to patients with no-event receiving higher weights combined with a smaller effective sample size. [redacted] Figure 18[redacted]

Figure 17: Unadjusted and population adjusted Kaplan–Meier curves for PFS

Key: MAIC, matching-adjusted indirect comparison; O-R, outcomes regression; PFS, progression-free survival.

Figure 18: Forest plot of hazard ratios of PFS for cemiplimab versus chemotherapy

Key: CI, confidence interval; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival. Note: naïve refers to the unadjusted indirect comparison

B.2.9.3.3. Response

The unadjusted and population adjusted response rates for cemiplimab, as well as the observed data from the Jarkowski 2016 study, are presented in Figure 19, with parameters from the outcomes regression presented and the distribution of weights used in the MAIC in Table 13 and Figure 21 of Appendix D.1.3.5. Both population adjustment methods led to a reduction of the effect associated with cemiplimab. [redacted] However, none of the methods showed statistical significance [Figure 20]

Figure 19: Unadjusted and population adjusted response rates

Key: MAIC, matching-adjusted indirect comparison; O-R, outcomes regression.

Figure 20: Forest plot of odds ratios of response for cemiplimab versus chemotherapy

Key: CI, confidence interval; MAIC, matching-adjusted indirect comparison; OR, odds ratio.
Note: naïve refers to the unadjusted indirect comparison.

B.2.9.4. Uncertainties in the indirect treatment comparisons

The evidence base for the interventions of interest consisted exclusively of single-arm trials and observational studies. Single-arm trials or observational studies on their own do not allow for between trial comparisons of treatment effects among competing interventions, as their treatment effects cannot be disentangled from their study effects. As no RCTs were identified, a standard NMA was not feasible. However, as with any analysis of single-arm trials, it is uncertain whether any unknown or unmeasured prognostic factors that are missing from the models may have influenced the outcomes of interest. The validity of both approaches (MAIC and STC) depends on how well the developed models describe the outcomes of interest. First, published information was used to identify important prognostic factors and guide the development of the models, which informed our base model including age, disease stage tumour differentiation and tumour location. Next, any covariates were added to the model that were identified in other existing prognostic models or those suggested by clinical experts. Despite our efforts to ensure the most appropriate models were used, it is important to acknowledge the models still rely on the assumptions and as such cannot be considered to be as valid as having RCTs for the interventions of interest.

An additional limitation is not all trials of interest reported baseline values for the factors in the prediction models. To mitigate this the process to identify and select covariates for the models was designed to be inclusive, ensuring that adjustments for the relevant factors were accounted for in the analysis wherever possible. The

models were estimated for each external study to align with the covariates reported in each trial. Despite these efforts, it is important to recognise it was not possible to adjust for all covariates across the trials. For example, many trials did not report information regarding tumour grade despite the established importance of this prognostic factor. Although the remaining covariates are expected to be correlated to covariates that were not reported, there is a risk that predicted cemiplimab outcomes would have differed had this information been available. All comparator studies, including Jarkowski et al which was relevant to the decision problem, reported at least two of the prognostic factors included in our model.

Research suggests that STC may provide some advantages over MAIC in the context of the current research question. It is important to highlight there were only 108 patients included in the cemiplimab trials for the analysis. NICE mentioned in their Decision Support Unit (DSU) guidance document that in the published MAICs at that time, the effective sample size was reduced by 80% of the original sample size on average where reported (n=3 studies). In this analysis of chemotherapy, the effective sample size reduced by 65.7% when looking at OS. The risk with such reductions is that MAIC results can be based on a small number of individuals due to the reweighting of individuals in the original sample. This issue was evident in this analysis, where weighted KM curves resulted in sudden drops in the curve due to large weights being attributed to specific individuals. Beyond the limited face validity of such results, the implications of fitting parametric models or extrapolating these results in cost-effectiveness analysis (CEA) are unclear. In the current context, where the CEA model for this study required survival estimates to be extrapolated to a lifetime horizon (that is 30 years), changes in KM curves due to reweighting may have profound implications for cost-effectiveness results. For this reason in the cost-effectiveness analysis a conservative approach is followed whereby the naïve unadjusted cemiplimab data are used in the base case with the adjusted STC data used in a scenario analysis.

B.2.9.5. Conclusion

Due to the limitations of the identified evidence base, and as per NICE guidance, an STC and MAIC were conducted to inform the comparative efficacy of cemiplimab versus current standard of care. Both methods used in this analysis align with

recommendations from the DSU guidance for population adjusted indirect comparisons and can be considered as the best attempt to account for between study differences given the challenge of evaluating comparative efficacy on the basis of single-arm clinical trials. However, as with any analysis of single-arm trials, it is uncertain whether any unknown or unmeasured prognostic factors missing from the models may have influenced the outcomes of interest.

Despite the above limitations, the results of the ITC showed [redacted]

When looking at response, [redacted]. These results are consistent with the clinical view of chemotherapy that although response rates are generally good, responses are often not durable and therefore survival benefits are limited.

In conclusion, for patients with advanced CSCC, a population adjusted indirect comparison using single-arm trial evidence from two single-arm cemiplimab studies and one single-arm chemotherapy study suggests that cemiplimab is likely to improve overall and progression-free survival compared to chemotherapy. However, in the absence of an RCT, given the number of assumptions and possible differences between studies that could not be adjusted for with the statistical methods, these findings need to be interpreted with caution.

B.2.10. Adverse reactions

No other studies outside of Phase II EMPOWER-CSCC 1 and the Phase I study were identified that provided additional safety data for cemiplimab. The primary analysis of integrated safety is based on the safety analysis set, defined as all

patients with advanced CSCC who received at least 1 dose of cemiplimab monotherapy in either study, on or before the data cut-off date defined for each study. The safety analysis set, therefore, also includes patients in the Phase II EMPOWER-CSCC 1 who received a 350mg flat dose of cemiplimab (n=23 patients).

Safety analyses for the Phase I and Phase II studies are separately presented in Appendix F.1. Additional safety analyses for a wider population who have received treatment with cemiplimab are presented in Appendix F.2.

B.2.10.1. Treatment exposure

A summary of treatment exposure is presented in Table 11.

At the time of data cut-off, 163 patients had received cemiplimab monotherapy for a mean of [redacted], with [redacted] patients ([redacted]%) receiving treatment for ≥24 weeks.[44] A mean of [redacted] doses were administered to the advanced CSCC population, with [redacted]% of patients receiving ≥[redacted] doses.

Table 11: Treatment exposure, safety analysis set

	Integrated analysis (N=163)	Phase I Study (N=26)	Phase II EMPOWER-CSCC 1 (N=137)
Duration of exposure, mean weeks (SD)	[redacted]	[redacted]	[redacted]
Doses administered, mean (SD)	[redacted]	[redacted]	[redacted]
Number of doses administered, n (%):			
≥0	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]
≥6	[redacted]	[redacted]	[redacted]
≥12	[redacted]	[redacted]	[redacted]
≥18	[redacted]	[redacted]	[redacted]
≥24	[redacted]	[redacted]	[redacted]
Cumulative dose administered, mean mg (SD)	[redacted]	[redacted]	[redacted]
Relative dose intensity, mean (SD)	[redacted]	[redacted]	[redacted]

Key: CSCC, cutaneous squamous cell carcinoma; NR, not reported; SD, standard deviation.
Source: Sanofi data on file, 2018[44]; Phase II EMPOWER-CSCC 1 CSR, 2018[45]; Phase I study CSR, 2018.[46]

B.2.10.2. Adverse events

A summary of TEAEs is presented in Table 12.

A total of [redacted] patients experienced at least one TEAE, including [redacted] patients ([redacted]%) with at least one Grade ≥3 TEAE and [redacted] ([redacted]%) patients with at least one SAE.[44] A total of eight (5%) patients discontinued the study drug due to TEAEs. TEAEs resulted in death for 7 (4.3%) patients. One of these deaths was considered by the investigator to be related to study treatment.

Table 12: Summary of adverse events, safety analysis set

	Integrated analysis (N=163)	Phase I Study (N=26)	Phase II EMPOWER-CSCC 1 (N=137)
Any TEAE, n (%)	[redacted]	[redacted]	[redacted]
Grade 3–5	[redacted]	[redacted]	[redacted]
Any SAE, n (%)	[redacted]	[redacted]	[redacted]
Discontinuations due to TEAEs, n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to drug interruption/delay, n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to a dose reduction, n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to death, n (%)	[redacted]	[redacted]	[redacted]

Key: CSCC, cutaneous squamous cell carcinoma; SAE, serious adverse events; TEAE, treatment-emergent adverse event.
Source: Sanofi data on file, 2018[44]; Phase II EMPOWER-CSCC 1 CSR, 2018[45]; Phase I study CSR, 2018.[46]

In the advanced CSCC population, the most frequently reported classes of TEAEs were [redacted].[44] Specifically, the most frequently reported AEs were [redacted]), as presented in Table 13. A total of [redacted]% of patients experienced at least one Grade ≥3 TEAE with [redacted] being the most commonly reported.

Table 13: Summary of common treatment emergent adverse events (≥5% of any grade ≥1% of Grade 3/4/5 in any group in the integrated analysis), safety analysis set

	Integrated analysis (N=163)		Phase I Study (N=26)		Phase II EMPOWER-CSCC 1 (N=137)	
	All grades	Grade 3/4/5	All Grades	Grades 3/4/5	All grades	Grades 3/4/5
Patients with a TEAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Integrated analysis (N=163)		Phase I Study (N=26)		Phase II EMPOWER-CSCC 1 (N=137)	
	All grades	Grade 3/4/5	All Grades	Grades 3/4/5	All grades	Grades 3/4/5
Musculoskeletal and connective tissue disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failure to thrive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Integrated analysis (N=163)		Phase I Study (N=26)		Phase II EMPOWER-CSCC 1 (N=137)	
	All grades	Grade 3/4/5	All Grades	Grades 3/4/5	All grades	Grades 3/4/5
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Integrated analysis (N=163)		Phase I Study (N=26)		Phase II EMPOWER-CSCC 1 (N=137)	
	All grades	Grade 3/4/5	All Grades	Grades 3/4/5	All grades	Grades 3/4/5
Blood and lymphatic system disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Delirium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Integrated analysis (N=163)		Phase I Study (N=26)		Phase II EMPOWER-CSCC 1 (N=137)	
	All grades	Grade 3/4/5	All Grades	Grades 3/4/5	All grades	Grades 3/4/5
Hepatobiliary disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune hepatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSCC, cutaneous squamous cell carcinoma; NR, not reported.
Source: Sanofi data on file, 2018[44]; Phase II EMPOWER-CSCC 1 CSR, 2018[45]; Phase I study CSR, 2018.[46]

A total of [redacted]% of patients experienced TEAEs considered by the investigator to be related to the study drug; the most frequent of which were [redacted]).[44] SAEs occurred in [redacted] with the most common being [redacted]

A total of [redacted]%) with advanced CSCC died with the most common primary cause [redacted].[44] TEAEs resulted in death for [redacted].

irAEs were reported by [redacted] with [redacted] having a Grade ≥3 irAE.[44] The most frequent irAEs were [redacted]).

B.2.10.3. Safety overview

The overall safety profile of cemiplimab for the treatment of advanced CSCC is consistent with that seen in other PD-1 inhibitors and across patient populations.[47] Cemiplimab has been shown to have a predictable safety profile with no new concerns identified at present. Furthermore, the safety database includes 76 patients who were treated for 24 weeks or longer and 33 patients treated for 48 weeks or longer, providing a duration of exposure adequate to characterise the safety profile of cemiplimab.

Overall, cemiplimab is associated with rates of [redacted].[44] Cemiplimab was generally well tolerated with only [redacted] of patients discontinuing treatment due to AEs. Furthermore, [redacted] of patients reported an irAE, [redacted]. As experience and familiarity with immunotherapy treatment grows, quick and effective management of common side effects is likely to continually improve; this is supported by risk management measures outlined in the draft SmPC.

The tolerability profile of immunotherapies such as cemiplimab over currently used chemotherapy is well accepted, with the documented AE profile of platinum-based

chemotherapy likely to have a substantial negative impact on patient QoL in a disease state with an already high burden. A recent meta-analysis of 3450 patients receiving PD-1/PD-L1 inhibitors demonstrated higher risk of all-grade rash, pruritus, hypothyroidism, hyperthyroidism, colitis, aminotransferase elevations, and pneumonitis but lower risk of all-grade AEs in general and lower risk of all-grade fatigue, sensory neuropathy, diarrhoea, hematologic toxicities, anorexia, nausea, and constipation, and treatment discontinuation when compared to traditional chemotherapy.[60] Furthermore, as most advanced CSCC patients are older, have co-morbid conditions and have exhausted other treatment options, cemiplimab offers an alternative treatment option with a different side effect profile to chemotherapy that may be preferable for these patients.

As a result of the high unmet need in advanced CSCC Sanofi has prepared a UK Named Patient Supply (NPS) programme for unsolicited requests of cemiplimab in advanced CSCC. This will allow clinicians access to cemiplimab (at the anticipated licensed dose of 350mg every 3 weeks) for the treatment of advanced CSCC patients prior to commercialisation, on a named patient basis. While formal data collection is not permitted from a regulatory stand point, the safety of cemiplimab at the flat 350mg dose in a real-world setting will be monitored. Sanofi estimates approximately 30 patients in the UK (with around 25 in England) will be enrolled in the NPS programme. This will be the first time cemiplimab will be used in the UK.

In summary, cemiplimab demonstrates a favourable benefit-risk profile for the treatment of advanced CSCC with a well-established and clinically manageable safety profile. This is likely to represent a significant improvement in patient burden relative to BSC and also current off licensed treatment options. Further safety data for both cemiplimab and comparators of interest are presented in the economic model and discussed in Section B.3.4.4.

B.2.11. Ongoing studies

Both the Phase II EMPOWER-CSCC 1 study and the Phase I study described within this submission are ongoing. [redacted]

A retrospective chart review study is also ongoing, aimed at gaining a better understanding of the current management and outcomes of ~600 advanced CSCC patients in the US and EU, including in the UK. This study will evaluate both clinical outcomes, including OS, PFS and ORR, alongside patient characteristics for advanced CSCC patients. It is proposed that this data alongside mature data from the cemiplimab trial programme could be incorporated into a DCA were cemiplimab to be recommended for use via the CDF. Further details of the proposed data collection are available in Appendix O.

B.2.12. Innovation

Cemiplimab will be the first and only approved systemic therapy that has demonstrated a substantial and durable tumour shrinkage, representing a 'step-change' in the management of advanced CSCC for clinicians and patients. Indeed, cemiplimab was granted 'breakthrough designation' from the US Food and Drug 0Administration (FDA) due to the substantial improvement on a clinically significant endpoint over available therapies.[61] The cemiplimab clinical trial programme is the largest prospective data set available to date with cemiplimab being the only treatment to have undergone a systematic and comprehensive benefit-risk assessment, yielding a positive outcome.

Cemiplimab offers a treatment option with a novel mechanism of action compared to currently used chemotherapy and BSC. For those patients with advanced CSCC who currently have no other options, cemiplimab offers a treatment option with related health benefits such as improved survival and DoR. Although these benefits will be captured in the quality-adjusted life year (QALY) calculation, their significance to patients should be viewed as both important and innovative. The curative potential associated with immunotherapies such as cemiplimab, and the possible return to normal living that this offers patients (in contrast to BSC or chemotherapy, which has shown limited results) should not be underestimated. The visual difference seen in patients after receiving cemiplimab (as presented in Figure 9 and Figure 10) can reasonably be expected to improve the HRQL of patients. Furthermore, by receiving an active treatment option, the psychological burden of waiting for the disease to worsen is alleviated and patients can begin to feel some hope for the future.

As a treatment for advanced CSCC, cemiplimab has the potential to make a significant difference not only in survival but also in relieving the significant disease and patient burden relative to currently used treatments. As such, a decision making process closely aligned with the regulatory timings will ensure patients who develop advanced CSCC will have access to an effective, licenced treatment option. Integration into the CDF would allow patients to begin receiving the benefits of this treatment immediately, while ongoing prospective data collection would appease the uncertainty seen with the current evidence.

B.2.13. Interpretation of clinical effectiveness and safety evidence

There are currently no approved systemic therapies for advanced CSCC patients, with clinicians relying on either small studies in CSCC, or studies in completely different solid tumours in addition to their own clinical experience.[5] Thus, patients are limited to using cytotoxic agents and targeted therapies which have limited or anecdotal evidence in CSCC, limited clinical activity and unknown risks. There is a clear unmet need for a treatment that has demonstrated improvement in disease control for patients with advanced CSCC who are at the end of their lives. Cemiplimab is the first treatment for patients with advanced CSCC to demonstrate clinically compelling efficacy, as demonstrated by high response rates, clinically meaningful durability of responses and potential for long-term survival.[47]

In patients with advanced CSCC, cemiplimab demonstrated a substantial and durable tumour response, with an ORR of [redacted] of note, [redacted]% of patients reported a benefit after treatment with cemiplimab (that is CR, PR or SD).[41] DoR was reported to be [redacted] for patients receiving cemiplimab, with [redacted]% of responders still in response at the time of the last disease assessment, further demonstrating the durability of response seen with this treatment. Maximal, or near maximal, depths of responses were often evidenced in the first response assessment at Week 8 and responses usually persisted and sometimes deepened; median TTR was just [redacted].[41]

In addition to the high tumour responses seen with cemiplimab, impressive survival was also demonstrated with median 12-month OS rate of [redacted] and 12-month PFS rate of [redacted]. It should be noted [redacted]

[redacted].[41] Cemiplimab also demonstrated consistent response in terms of the primary endpoint (ORR) and survival improvement across analyses in both laCSCC and mCSCC patients. [redacted]

Currently available data for cemiplimab [redacted]. Nevertheless, the notable reduction in visual disfigurement seen with cemiplimab, and the potential effect this may have on quality of life, should not be underestimated. Furthermore, by receiving an active treatment option, the psychological burden of waiting for the disease to worsen is alleviated and patients can begin to feel some hope for the future.

The overall safety profile of cemiplimab is consistent with that seen in other PD-1 inhibitors and across patient populations, with no new safety concerns identified. Overall, cemiplimab was associated with low rates of [redacted].[44] Only 5% of patients discontinued treatment due to an AE and less than a quarter of patients reported an irAE, most of which were Grade 1–2, further demonstrating the tolerability of this treatment.

B.2.13.1. Strengths and limitations of the clinical evidence base

Overall, the clinical evidence base available provides an appropriate base to inform the assessment of clinical effectiveness of cemiplimab for the treatment of advanced CSCC, particularly in the context of the CDF. The integrated analysis presented provides the largest prospective data set in advanced CSCC, enrolling a total of 163 patients.

Both studies, which fed into the integrated analysis, were conducted in line with GCP guidelines, with steps taken to minimise bias and independent monitoring or advisory committees in place to provide oversight of safety and efficacy considerations, study

conduct and risk-benefit ratio. The Phase II EMPOWER-CSCC 1 study was primarily designed to assess ORR, OS and PFS, key outcomes of direct relevance to clinical practice. With regard to response, when assessing the benefit of cemiplimab in practice, this will largely be based on clinical judgement, with consideration given to the potential of response despite an initial increase in tumour burden. Patients were permitted to receive treatment beyond RECIST-defined progression as a reflection of this practice (see Section B.2.5).

Both studies are generally reflective of patients presented for treatment of advanced CSCC in UK clinical practice, with trial results anticipated to be reflective of the advanced CSCC population. It should be noted, however, that there were no UK sites in either trial and clinical experts felt trial patients were generally fitter and younger than would be seen in UK clinical practice. This is often the case in clinical trials, however, and results of trials are still generalisable to UK practice.

Importantly, the efficacy data presented within this submission is based on a 3mg/kg every two weeks (q2w) dose of cemiplimab. Over the course of the cemiplimab development programme, a fixed 350mg every three weeks (q3w) dosing regimen was introduced and it is this latter dose which is expected to be the licenced dose. The q3w dosing interval was selected as it has the advantage of less frequent dosing.[47] Safety and efficacy data from the 3 mg/kg q2w regimen have been used to support the proposed dose regimen (350 mg q3w) based on pharmacokinetic (PK) modelling and simulation of exposure, and supported by observed data at 350 mg q3w. The analyses used to support the PK bridging are as follows: The available concentration data from 505 patients who received cemiplimab are characterised by a population PK model. Comparison of simulations of drug concentration is used to illustrate the similarity in exposure and between-patient variability between the 3 mg/kg Q2W and 350 mg q3w dosing regimens. Finally, observed concentration data for the 350 mg q3w regimen are compared to the simulated profiles for the same regimen, to confirm the predicted exposure. The population PK analyses demonstrate that the 350mg q3w regimen achieves exposure and between-patient variability similar to the 3mg/kg q2w dosing regimen. This supported bridging of the data sets, enabling the use of PK, safety and efficacy data from patients receiving

3mg/kg q2w, to support the 350mg q3w regimen. Additional data collection at the 350mg q3w dose is ongoing.

Both cemiplimab trials were single-arm studies, reflective of the rarity of eligible patients, the lack of an accepted standard of care and difficultly in recruitment to a comparative Phase III trial; comparative efficacy has therefore been made through naïve comparison and population adjusted ITCs (see Section B.2.9).

The data for cemiplimab is associated with a number of uncertainties. As previously mentioned, these consist of the lack of Phase III randomised trials due to the small patient population and lack of licensed comparator treatments in this rare disease, no head to head comparative data was available and current efficacy and safety data is immature, based on a follow-up of less than 1 year. Furthermore, both studies presented within this submission have small patient populations.

In conclusion, cemiplimab is the first approved systemic treatment for advanced CSCC, achieving high levels of response in both laCSCC and mCSCC. Cemiplimab is generally well tolerated with a rate of serious adverse reactions comparable to other PD-1/PD-L1 therapies. Cemiplimab has the potential to make a significant difference not only in survival but also in relieving the significant disease and patient burden relative to currently used treatments.

B.2.13.2. End-of-life considerations

Cemiplimab fulfils the two criteria specified by NICE to qualify as an end-of-life treatment option. Table 14 summarises how these criteria are met.

Table 14: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS was reported at 15.1 months in a retrospective chart review of advanced CSCC patients receiving platinum-based chemotherapy.[6] In the same study 100% of patients not receiving platinum chemotherapy had died by 12 months (median OS = 3.5 months; n=7). Furthermore, clinicians consulted at an advisory board indicated that survival for advanced CSCC patients in the UK would not exceed 5% at 2 years.	Section B.1.3 (Page 23)
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	[redacted] Modelled results for cemiplimab show a survival benefit of [redacted] months compared to current treatment.	Section B.2.6.2 (Page 52) and Section B.3.7.1 (Page 151)
Key: CSCC, cutaneous squamous cell carcinoma; NHS, National Health Service; OS, overall survival.		

B.3. Cost effectiveness

- A partitioned survival model compared cemiplimab with chemotherapy or best supportive care in patients with advanced CSCC.
- Clinical efficacy and safety data for cemiplimab were derived from an integrated analysis (a pooled analysis) of data from the Phase I and Phase II cemiplimab clinical trials.
- A naïve unadjusted comparison of cemiplimab with available data for chemotherapy was used to inform the base case. Given no data was identified for BSC, chemotherapy data was also used to inform cost-effectiveness estimates versus BSC.
- PFS and OS were modelled independently for cemiplimab and chemotherapy, alternative parametric models were fitted to the observed data. The best fitting models that produced clinically plausible long term estimates were used in the base case.
- Given the expected uncertainty stemming from the available evidence, an effort was also made to formally elicit clinical experts' opinion on the long-term survival estimates of both cemiplimab and chemotherapy. This was incorporated into a scenario analysis.
- A 22-month stopping rule was applied to cemiplimab treatment in line with the phase II trial protocol followed by a continuation of the treatment benefit for up to 3 years.
- To estimate the utility pre- and post-progression for patients with advanced CSCC expressed in EQ-5D values, the Longworth *et al.* (2004) mapping algorithm was used to convert the EORTC QLQ-C30 values derived from the Phase II EMPOWER-CSCC 1 study to EuroQol 5-Dimension 3-Level (EQ-5D-3L).
- Only direct healthcare costs were included from a National Health Service (NHS) perspective.
- In the context of CDF (and the proposed CAA), base case cost-effectiveness estimates, utilising a credible and clinically plausible set of assumptions for cemiplimab, are £43,740 and £46,239/QALY, versus chemotherapy and BSC, respectively.
- Probabilistic sensitivity analysis suggests that at a willingness to pay threshold of £50,000/QALY, cemiplimab would be cost effective in ~55% of cases versus chemotherapy and in ~50% of cases versus BSC, demonstrating the level of uncertainty associated with the currently available evidence.
- An extensive range of deterministic and scenario analyses demonstrate in the majority of scenarios incremental cost-effectiveness ratios (ICERs) remain below £50,000/QALY.
- Although uncertainty remains, cemiplimab is likely to be a cost-effective end-of-life treatment for this underserved patient population.
- Collection of data, whilst on the CDF, would increase the certainty surrounding these cost-effectiveness estimates whilst allowing access to cemiplimab for patients with a very high unmet need and for whom there are no licenced or effective alternatives.

B.3.1. Published cost-effectiveness studies

A SLR was conducted to identify existing economic analyses in CSCC. The SLR was initially undertaken in October 2017. Searches were rerun in September2018 with no studies of relevance to the decision problem identified. A detailed description of the SLR is provided in Appendix G.

MEDLINE and Embase were searched for relevant economic evaluations along with the following sources: Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts or Reviews of Effects, Cochrane Methodology Register, American Economic Association, EconLit, NHS Economic Evaluation Database and health technology assessments (HTAs). The SLR included a review of the grey literature, which captured data from sources that were not indexed in the literature databases but were available on websites for HTA bodies.

A summary of the eligibility criteria used for the systematic review of economic evaluations in advanced CSCC is provided in Table 15.

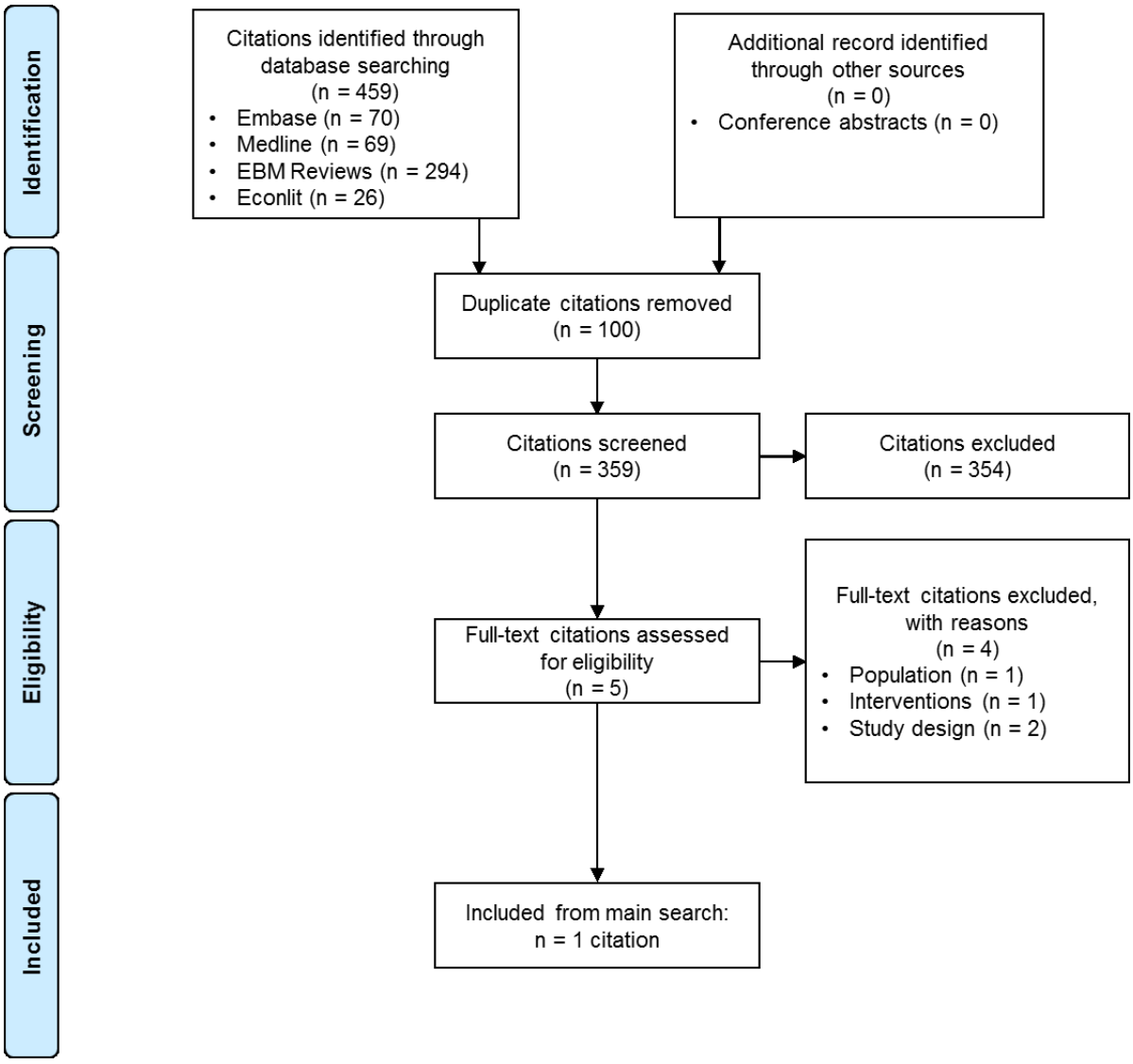
Table 15: Eligibility criteria for economic evaluations in advanced cutaneous squamous cell carcinoma

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adult patients with cutaneous squamous cell carcinoma who: – have locally advanced disease and who are not candidates for surgery, or – have developed nodal and/or distant metastases	• Adult patients with other skin cancers (for example basal cell carcinoma, melanoma) or squamous cell carcinomas (for example head and neck). • Adult patients with local or locally advanced cutaneous squamous cell carcinoma who are candidates for treatment with surgery and/or radiation.
Intervention/Comparator	• No restriction on inclusion of studies based on interventions or comparators. • All pharmacological interventions to be captured.	• Studies assessing non-drug treatments (for example surgery, RT).
Outcomes	• Studies including a comparison of benefits and costs between the intervention and comparator arms: – results should be expressed in incremental costs, incremental cost-	• Utility data only

Criteria	Inclusion criteria	Exclusion criteria
	effectiveness ratios, quality adjusted life years, life years gained, or any other measure of effectiveness reported together with costs. • Studies reporting on the costs associated with treating cutaneous squamous cell carcinoma.	
Study design	• Cost-effectiveness analysis • Cost–utility analysis • Cost–benefit analysis • Cost-minimisation analysis • Budget impact models • Cost–consequence studies • Cost-of-illness studies	• Epidemiological studies • Clinical studies • Pharmacokinetic/ Pharmacodynamic (Animal/ *in vitro*) study • General quality of life studies
Other	• Studies published in English • No time limits	• Studies not published in English
Key: RT, radiotherapy.		

The review process is summarised in the PRISMA diagram presented in Figure 21. No economic models were identified that evaluated the cost-effectiveness of any interventions for the target population, though one study which modelled the cost of treating patients with skin cancer, including CSCC patients with nodal involvement, was identified. This study was conducted in South Africa[62] and did not separate CSCC and basal cell carcinoma (BCC), patients, therefore it was not applicable to this economic analysis.

Figure 21: PRISMA diagram for the systematic literature review of economic evaluations in advanced cutaneous squamous cell carcinoma



Key: EBM, Evidence Based Medicine; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

B.3.2. Economic analysis

Given there are no existing economic analyses of cemiplimab in advanced CSCC, a *de novo* economic analysis is provided below to assess the cost-effectiveness of cemiplimab for the treatment of patients with advanced CSCC.

The de novo cost-effectiveness analysis was conducted from an NHS England perspective over a lifetime time horizon using a discounting factor for both costs and utilities of 3.5% in line with the NICE reference case.[63]

B.3.2.1. Patient population

The population considered for this submission comprises patients with advanced CSCC defined as patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiotherapy.

The cost-effectiveness analyses presented in this appraisal are based on pooled data from mCSCC and laCSCC patients, thus reflecting the overall advanced CSCC population in the Phase I and Phase II cemiplimab trials. Pooling these patient groups was considered appropriate for a number of reasons, as outlined in Section B.2.3.1.3.

Therefore, the population under consideration for this appraisal reflects the patient groups in clinical studies of cemiplimab, the anticipated licenced indication and the expected use of cemiplimab in the UK.

B.3.2.2. Model structure

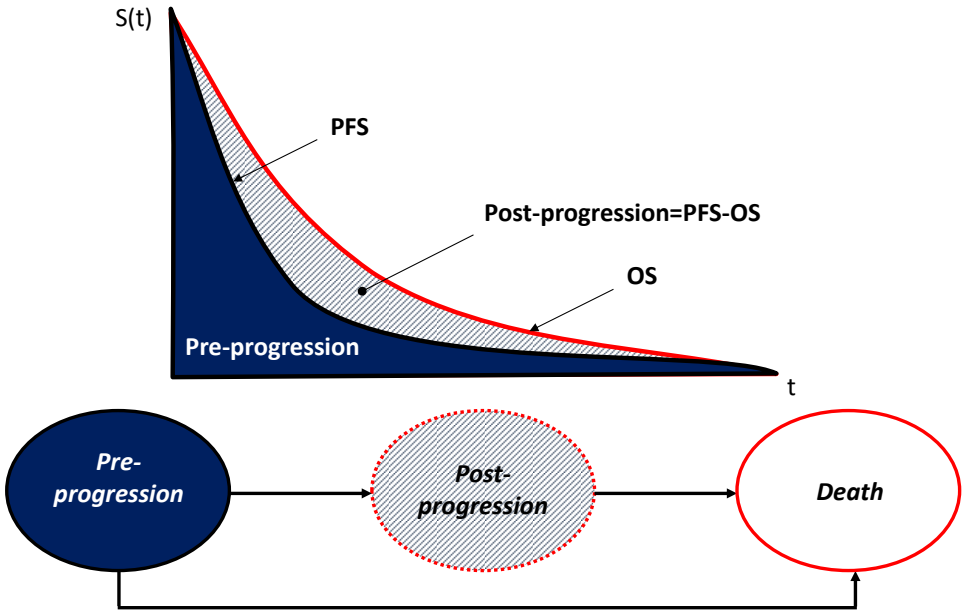
The cost-effectiveness model was programmed in Microsoft Excel® and designed based on a 'partitioned survival' structure (otherwise known as 'area-under-the-curve [AUC]' structure). A schematic of the cost-effectiveness model structure is presented in Figure 22.

Patients begin in the pre-progression health state where they receive either cemiplimab or a comparator treatment and are stable or responding to the therapy. Patients in this state would also receive background BSC consisting of visits to healthcare experts, blood tests, wound management and palliative treatment. Over time, patients transitioned directly to the death state or the post-progression health state where they received only BSC before moving to the death state. Costs related to BSC were assigned to all patients for the duration of time spent in the pre-progression or the post-progression health states.

The proportion of patients in the pre-progression health state reduced over time according to the treatment-specific (time-varying) hazard rates at which patients leave this state, which corresponds to PFS time. The proportion of patients that died increased over time according to (time-varying) treatment specific death rates corresponding to OS times. The difference between the proportion of patients alive and proportion of patients in the pre-progression health state defined the proportion of patients in the post-progression health state at any point in time. The proportions of patients in the pre- and post-progression health states were multiplied with corresponding utility estimates (discounted over time) and summated over time to obtain treatment-specific estimates of expected QALYs. Similarly, expected costs by treatment were calculated given treatment received and resource use associated with pre- and post-progression health state distributions (again discounted over time).

It is worth noting that functionality for incorporation of response rates per treatment arm was initially considered for the cost-effectiveness model. However, since the relevant comparator studies identified in the SLR did not include survival estimates per level of response, it would not be possible to model the PFS according to response. Additionally, there is no evidence available to support differences in terms of costs or resources for responders versus non-responders. Thus, the addition of this functionality in the cost-effectiveness model was not explored further.

Figure 22: *De novo* cost-effectiveness model schematic



Key: OS, overall survival; PFS, progression-free survival.

The main advantage of the partitioned survival model approach versus the Markov approach is that it provides a much closer fit to the actual PFS and OS data (that is KM curves) as observed in the clinical trials. It allows the time dependency in the risk of events over time to be captured due to survival being modelled as a function of time since model entry. Although KM curves for cemiplimab are relatively immature, using an approach that aligns with the available data is important given that immunotherapies differ from traditional chemotherapies with respect to their mechanism of action. In fact, as extensively discussed in NICE TA517[64], immunotherapies are associated with long-term survival patterns such as the plateauing of OS and PFS curves indicating a decreasing probability of progression and death for a certain proportion of patients. Cemiplimab, as a PD-1 inhibitor, is expected to demonstrate similar long-term survival patterns; as a result, the structure needs to be sufficiently flexible to align closely with the available data and allow for exploration of these patterns.

The Decision Support Unit (DSU) highlights several potential issues that can be encountered with partitioned survival models and has made recommendations on how such models should be reported so the impact of these can be adequately

assessed. These recommendations, along with how they were accounted for in this analysis, are summarised in Table 16.

Table 16: Decision Support Unit recommendations for time-in-state models and application in the cemiplimab economic analyses

DSU recommendation	Application in analysis
Report model conceptualisation with rationale for the 'Partitioned survival analysis'	• A partitioned survival analysis approach was followed to reflect the natural history of the disease and allow for the structural flexibility needed.
Summarise key assumptions	• PFS and OS were modelled/extrapolated independently. • Trends in hazard of PFS and OS are explored through a series of sensitivity analyses.
Recognise limitations for extrapolation	• No underlying explicit disease process. • Challenge to explore relationship between treatment effect pre- and post-progression.
Consider all relevant evidence for extrapolation	• Given the limited survival data available at the time of this submission, long-term survival estimates were formally elicited from clinical experts in order to validate the extrapolation methods in the cost-effectiveness model
Present within-trial survival curves for individual clinical events	• Kaplan–Meier curves from cemiplimab studies for PFS and OS are presented.
Present alternative assumptions regarding extrapolation	Alternative assumptions used included: • Continuation of hazard based on observed effects in trial for different pre-specified periods (that is up to 22 months, 3 years or 5 years), then to equal to hazard of comparator treatment (chemotherapy). • Constant hazard (that is exponential, hazard extrapolated based on last hazard carried forward). • Application of a waning effect
Key: OS, overall survival; PFS, progression-free survival	

The economic modelling approach was validated both pre- and post-model development by clinical and health economic experts. Details of the validation process undertaken are presented in Section B.3.10.

A summary of the key features of the *de novo* economic analysis can be found in Table 17.

Table 17: Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	30 years (lifetime)	A 30 years' time horizon was deemed to be sufficiently long to capture the lifetime of patients with advanced CSCC. The modelled overall survival at 30 years based on the economic model was less than 0.01% for all treatment arms.
Treatment waning effect?	No	In the base case the continuation of the cemiplimab treatment effect after treatment is stopped at 22 months is assumed for up to 3 years after which point the hazard is set to be equal to the chemotherapy's hazard. Thus, in the base case no waning treatment effect is assumed. Further details on the cemiplimab treatment duration and subsequent treatment effect are discussed in Section B.3.3.3.1.
Source of utilities	EORTC-QLQ 30 values from the Phase II EMPOWER 1 study were mapped to EQ-5D-3L values	NICE reference case[63] Further details on the utilities used in the economic analysis can be found in Section B.3.4.
Source of costs	Published sources such as the NHS reference costs and PSSRU were used.	NICE reference case[63] Further details on the costs used in the economic analysis can be found in Section B.3.5.
Cycle length	1 month (30.4 days)	A 1-month cycle length was used in the economic model, given the KM curves were divided into monthly cycles to generate the discrete hazards for PFS and OS. The model included a half cycle correction.
Discount	3.5% both for costs and utilities	NICE reference case[63]
Perspective	NHS England perspective	NICE reference case[63]

Key: CSCC, cutaneous squamous cell carcinoma; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EQ-5D-3L, EuroQol 5-Dimension 3-Level; KM, Kaplan–Meier; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OS, overall survival; PFS, progression-free survival.

B.3.2.3. Intervention technology and comparators

Cemiplimab, a fully human anti-PD-1 monoclonal antibody (mAb), is the intervention under consideration for this economic analysis. Cemiplimab is considered within its anticipated marketing authorisation for the treatment of patients with advanced CSCC for the purposes of this appraisal.

Two different dosing regimens for cemiplimab were studied in the Phase II EMPOWER-CSCC 1 study: a 3mg/kg intravenous (IV) infusion q2w and a 350mg fixed dose IV infusion q3w. However, the recommended dosing regimen of cemiplimab in the anticipated marketing authorisation is expected to be 350mg q3w administered as an IV infusion over 30 minutes until symptomatic disease progression or unacceptable toxicity (Table 2). Treatment may be continued through initial measurable disease progression until symptomatic disease progression or unacceptable toxicity in order to maximise opportunity for patients to experience clinical benefit.[47] Therefore, in line with the anticipated marketing authorisation, in the cost-effectiveness model the fixed 350mg q3w cemiplimab dose is used for the base case analyses. Though, an additional functionality was also incorporated in the model to allow further exploration of different dosing regimens based on the 3mg/kg q2w weight-based cemiplimab dose.

For patients who develop advanced CSCC, treatment options are limited. Currently there are no licenced treatments available for this population in the UK. According to UK clinical oncologists, most advanced CSCC patients (~75%) would receive BSC constituting palliative care aimed at controlling the symptoms of the condition. However, some patients (~25%) may be fit enough to tolerate and therefore receive chemotherapy (cisplatin and 5-fluorouracil [5-FU] being the most common chemotherapy regimen), as discussed in Section B.1.3. As such, both BSC and chemotherapy are considered comparators in the economic analysis.

The SLR for efficacy and safety identified one relevant study for chemotherapy but no evidence was identified for BSC (as detailed in Appendix D.1). Given the lack of available evidence on BSC in advanced CSCC, in the base case the clinical data for chemotherapy was also used for BSC. This is likely to be a conservative assumption and was deemed an appropriate solution by UK clinical experts.

This SLR also identified data for a number of EFGR inhibitors (such as cetuximab). Anecdotal reports suggest that EFGR inhibitors are occasionally used in the UK for the treatment of advanced CSCC however as these therapies are not licenced or reimbursed in the UK for this indication they were not considered as appropriate comparators for this submission. However, given the lack of evidence to inform the efficacy of BSC, two additional sensitivity analyses were considered where the data from the EFGR inhibitor studies were used as a proxy for BSC. In the first analysis, EFGR inhibitors' studies were pooled together to create a proxy for BSC whereas in the second analysis all EFGR inhibitors' studies were pooled together alongside the study identified for chemotherapy to approximate BSC (Appendix P). Clinical opinion sought at the UK advisory board suggested that EGFRs were not expected to be effective in CSCC suggesting that these additional analyses are again likely be conservative.

B.3.3. Clinical parameters and variables

Clinical efficacy and safety data for cemiplimab in advanced CSCC used in the cost-effectiveness model was derived from an integrated analysis of data from the Phase I and Phase II EMPOWER-CSCC 1 clinical trials. This also formed the clinical evidence base of the EMA regulatory filing as described in Section B.1. This was also considered a reasonable approach by UK clinical experts, attending a UK advisory board, given the immaturity of the Phase II data and similarities in patients' baseline characteristics. Additionally, a formal experts' elicitation exercise was conducted to help reduce uncertainty and provide meaningful insight on the long-term impact of cemiplimab versus the current standard of care (described in detail in Section B.3.3.2.2).

The latest available evidence from the Phase II EMPOWER-CSCC 1 trial is based on an interim analysis from an October 2017 data cut. The median duration of follow up was 8.6 months (range: 0.8 to 15.9) for all 82 advanced CSCC patients in the FAS (see Section B.2.4). [redacted]

[redacted]

Clinical efficacy and safety parameters applied in the cost-effectiveness model are discussed in detail in the sections below and include:

- Baseline characteristics
- PFS and OS for cemiplimab and comparator therapies
- Treatment duration and stopping rules
- HRQL
- AEs

B.3.3.1. Model baseline characteristics

The baseline characteristics used in the cost-effectiveness model are in line with patient characteristics from the integrated analysis of the Phase I and the Phase II EMPOWER-CSCC 1 trials as presented in Section B.2.3.2. The key demographics used in the model are summarised in Table 18.

Table 18: Patient characteristics at baseline for the base case

		Parameter	Source/justification
Mean age – years (SD)		70.44 (11.2)	Mean age from Phase I and II (EMPOWER-CSCC 1) cemiplimab studies based on weighted-dose patients.
Gender (male) n (%)		85.0%	Estimate of gender ratio based on pooled data from Phase I and II (EMPOWER-CSCC 1) trials.
Males*	**Weight (kg), mean (SD)**	83.9 (15.3)	Pooled data from Phase I (n=26) and EMPOWER-CSCC 1 (n=82, SAF dataset) cemiplimab trials.
	Height (cm), mean (SD)	174.7 (6.6)	Pooled data from Phase I (n=26) and EMPOWER-CSCC 1 (n=82, SAF dataset) cemiplimab trials
Females*	**Weight (kg), mean (SD)**	62.1 (14.8)	Pooled data from Phase I (n=26) and EMPOWER-CSCC 1 (n=82, SAF dataset) cemiplimab trials.
	Height (cm), mean (SD)	158.6 (9.2)	Pooled data from Phase 1 (n=26) and EMPOWER-CSCC 1 (n=82, SAF dataset) cemiplimab trials.

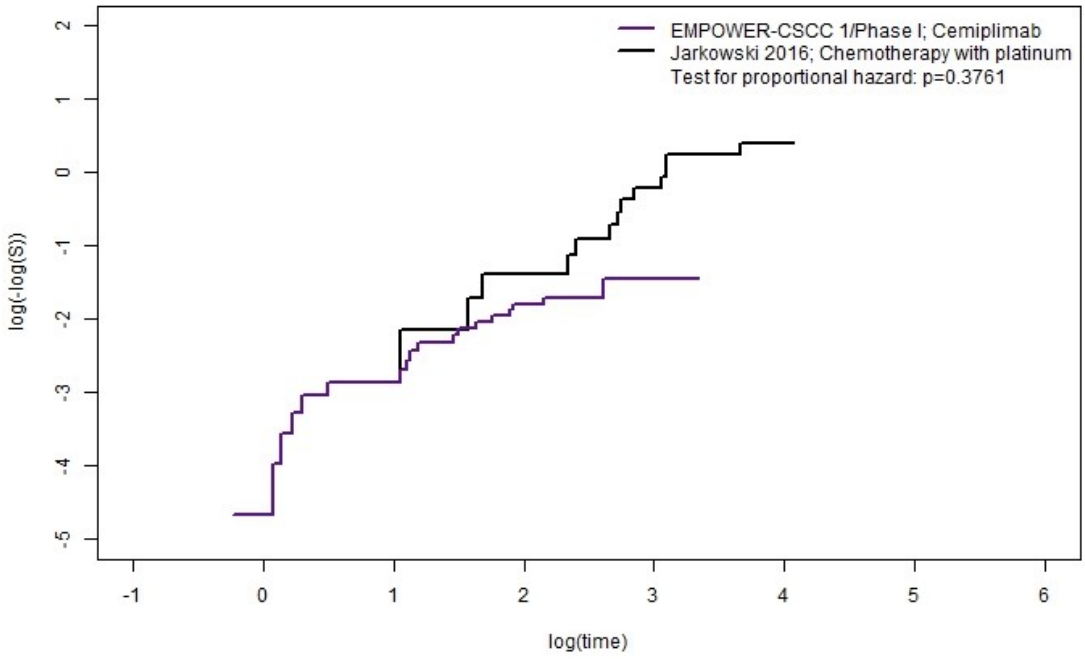
	Parameter	Source/justification
Key: SAF, Safety analysis set; SD, standard deviation. **Notes:** [a], Gender-specific height and weight estimates were used for the wastage calculations associated with weight-based treatments (please see details around the wastage calculations in Section B.3.5.1).		

B.3.3.2. PFS and OS

B.3.3.2.1. Approach to extrapolation of progression-free and overall survival

Since a lifetime time horizon is required for the for the AUC partitioned survival approach, it was necessary to extrapolate the available data until all patients have progressed or died. A pairwise framework is appropriate for the current decision problem comparing cemiplimab with the current standard of care in the UK; a flexible modelling approach was used where each intervention was modelled independently for both PFS and OS. Following inspection of the log cumulative hazard plots (Figure 23) and the consideration that the evidence base consists of only single-arm clinical trials and observational studies, it was considered most appropriate to fit alternative parametric models to the observed data for each intervention for PFS and OS, in line with the NICE DSU Technical Support Document (TSD) 14.[65] Furthermore, given that cemiplimab is a PD-1 with a different mechanism of action compared with chemotherapy, the proportional hazard assumption was not expected to be valid as previously shown in immunotherapy appraisals.[66-68]

Figure 23: Log cumulative hazard plot for overall survival



B.3.3.2.2. Process for fitting parametric models to each treatment arm for progression-free and overall survival

Alternative parametric models were fit to both the observed PFS and OS cemiplimab data (that is 'naïve comparison'), as well as the 'predicted' cemiplimab PFS and OS for each comparison base on the simulated treatment comparison as described in section B.2.9. The 'predicted' cemiplimab result from the STC corresponded to the chemotherapy comparator to align with the specific target population from the Jarkowski et al study.[6] Similarly, alternative parametric models were fit to the observed data for cemiplimab and chemotherapy. The process to select parametric distributions for PFS and OS for each intervention in the cost-effectiveness model involved the following steps:

1. Development of the hazard over time regarding PFS and OS in the relevant trials was visually inspected.
2. Log cumulative hazard plots versus log (time) or time were constructed for the trials of interest to inspect whether the hazards are likely to be non-monotonic, monotonic or constant.[69]

3. The following competing survival distributions were considered for PFS and OS:
    a. First-order fractional polynomials with exponent p_1=0 (Weibull) and p_1=1 (Gompertz).
    b. Second-order fractional polynomials with exponents p_1=0 or 1 and power p_2=-1, -0.5, 0, 0.5, or 1. These second-order fractional polynomial models are extensions of the Weibull and Gompertz models and allow arc and bathtub shaped hazard functions.
    c. Additionally, the lognormal and log-logistic distributions were considered.

    These distributions were considered sufficient to cover a broad spectrum of HR shapes spanning monotonically increasing and decreasing shapes to more complex U-shaped curves. The fit of the competing statistical models to the data was compared with the deviance information criteria (DIC). DIC is recognized as a generalization of the more commonly seen Akaike's Information Criterion/Bayesian Information Criterion scores. Furthermore, the DIC score is more appropriate given the Bayesian framework in which the hazards were generated.
4. The tails of the obtained PFS and OS functions were inspected to assess whether the extrapolation of PFS and OS beyond trial follow-up was in line with clinical expectations.

As well as the models described in Step 3, additional flexible models such as mixture cure models, explored in previous immunotherapy NICE submissions, were considered to extrapolate the survival data. However, given the immaturity of the observed data and in discussions with UK experts (3 clinical oncologists and 2 health economists) who attended the Sanofi advisory board meeting, it was determined additional complex approaches would not help provide any further clarity on the long-term survival of cemiplimab and comparators and would increase the risk of overfitting the available data. Instead, a formal experts' elicitation exercise was deemed more appropriate to help validate the extrapolated survival estimates described at Step 4.

As part of Step 4, the SHeffield ELicitation Framework (SHELF) was used to elicit the opinion of experts on what they expected long-term survival to be with both cemiplimab and chemotherapy. The results are further discussed in Sections

B.3.3.2.3 and B.3.3.2.5 with details around the methodology followed described in Appendix M.

PFS was restricted by OS (that is PFS≤OS) and the parametric distributions used for PFS were validated for clinical plausibility in relation to the OS results. In addition, the estimates resulting from the extrapolation of OS were checked for plausibility relative to the age adjusted mortality rates for the general population. OS was capped based on the general mortality rate in the UK.[70]

B.3.3.2.3. Progression-free and overall survival for cemiplimab based on observed data - naïve comparison (used in the base case)

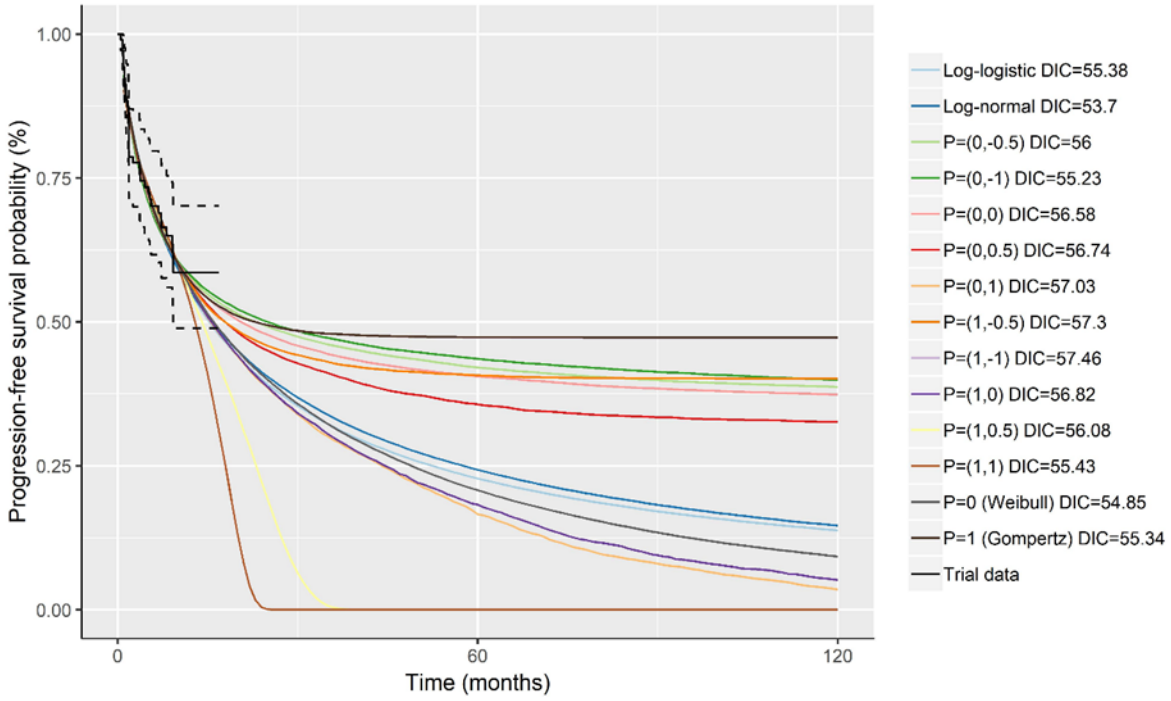
Figure 24 and Figure 25 summarise the estimated PFS and OS based on the alternative parametric distributions fitted to the observed cemiplimab data (i.e. 'naïve') for the overall population and include the DIC for each distribution. The goodness of fit and plausibility of alternative parametric distributions to extrapolate PFS and OS with cemiplimab are summarised in Table 19 and Table 20, respectively.

Given the limitations and uncertainty surrounding the results of the population adjusted comparison (see Section B.2.9.4), and the subsequent extrapolated survival estimates (see Section B.3.3.2.4), a 'naïve' approach was employed in the base case. In this 'naïve' approach distributions were fit to the observed cemiplimab data for the overall population. This approach was also deemed more appropriate since it produced conservative long term estimates for cemiplimab when compared with the ones produced with the adjusted comparison.

Best fitting distributions were considered to be those with the lowest DIC values (lower DIC value indicating a better fit to the source data) that also declined over time. Although a lognormal distribution provided the best fit based on DIC for both OS and PFS, it was only used to extrapolate the OS in the base case. For PFS extrapolations the Weibull distribution was used in the base case since it provided a good fit based on DIC but also generated slightly more conservative long term estimates when visually inspected.

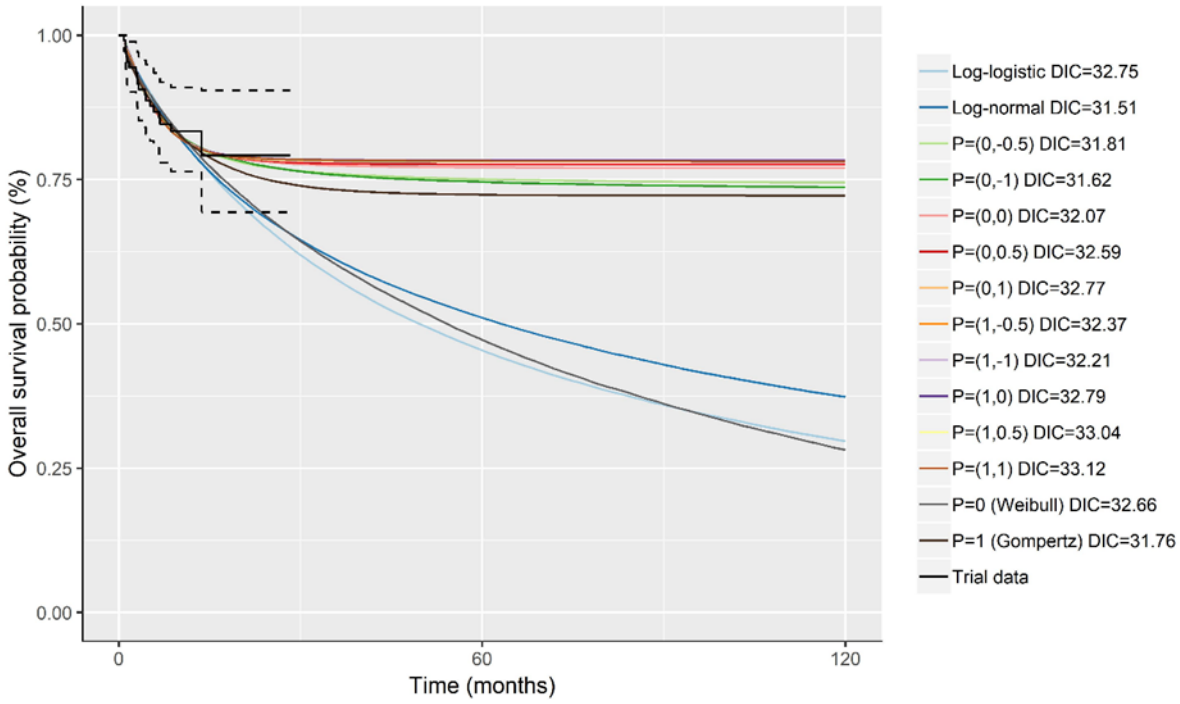
Distributions that declined over time were preferred for cemiplimab over curves that plateaued in the long-term. Although it is likely that cemiplimab would show a survival profile consistent with other PD1s (i.e. survival plateaus) given the observed data are limited for cemiplimab this approach was deemed to be more conservative. In the scenario analyses, Weibull or Gompertz and Lognormal or Log-Logistic distributions were explored for OS and PFS, respectively.

Figure 24: PFS curves for cemiplimab based on the naïve analysis of overall population from the integrated Phase I and II (EMPOWER-CSCC 1) trials



Key: DIC, deviance information criterion.

Figure 25: Overall survival curves for cemiplimab based on the naïve analysis of overall population from the integrated Phase I and II (EMPOWER-CSCC 1) trials



Key: DIC, deviance information criterion.

Table 19: Goodness of fit and plausibility of alternative parametric distributions used to estimate PFS curves with reference treatment (cemiplimab)

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	PFS at 60 months	Extrapolation
Weibull (P1=0)	54.85	✓✓	21%	Decreases over time
Second-order fractional polynomial P1=0, P2=-1	55.23	✓	44%	Decreases over time
Second-order fractional polynomial P1=0, P2=-0.5	56.00	✗	42%	Plateaus after 36 months
Second-order fractional polynomial P1=0, P2=0	56.58	✗	41%	Plateaus after 36 months
Second-order fractional polynomial P1=0, P2=0.5	56.74	✗	36%	Plateaus after 48 months
Second-order fractional polynomial P1=0, P2=1	57.03	✗✗	17%	Decreases over time
P1=1 (Gompertz)	55.34	✓	47%	Plateaus after 24 months
Second-order fractional polynomial P1=1, P2=-1	57.46	✗✗	47%	Plateaus after 24 months
Second-order fractional polynomial P1=1, P2=-0.5	57.30	✗✗	41%	Plateaus after 36 months
Second-order fractional polynomial P1=1, P2=0	56.82	✗	18%	Decreases over time
Second-order fractional polynomial P1=1, P2=0.5	56.08	✗	0%	Plateaus after 36 months

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	PFS at 60 months	Extrapolation
Second-order fractional polynomial P1=1, P2=1	55.43	✘	0%	Plateaus after 24 months
Log-normal	53.70	✓✓✓	24%	Decreases over time
Log-logistic	55.38	✓	23%	Decreases over time

Table 20: Goodness of fit and plausibility of alternative parametric distributions used to estimate overall survival curves with reference treatment (cemiplimab)

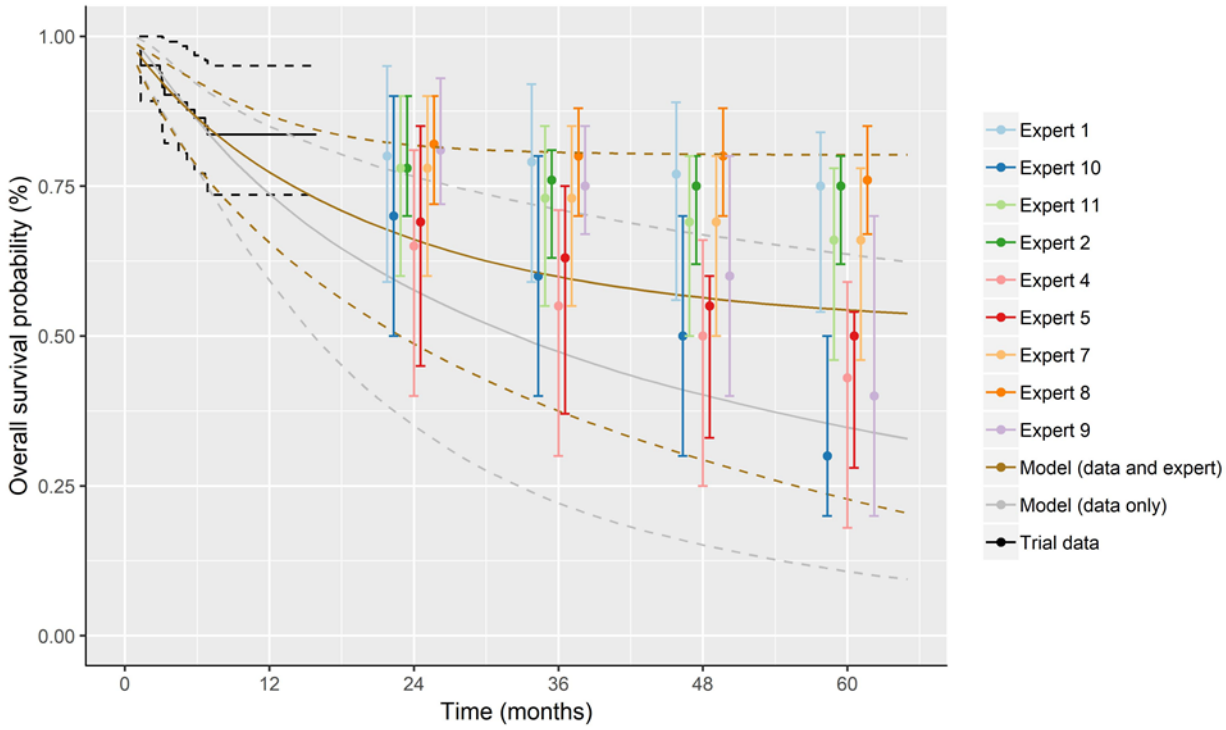
Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
Weibull (P1-0)	32.66	✓	48%	Decreases over time
Second-order fractional polynomial P1=0, P2=-1	31.62	✓✓	75%	Plateaus after 24 months
Second-order fractional polynomial P1=0, P2=-0.5	31.81	✓✓	75%	Plateaus after 24 months
Second-order fractional polynomial P1=0, P2=0	32.07	✓	77%	Plateaus after 24 months
Second-order fractional polynomial P1=0, P2=0.5	32.59	✓	78%	Plateaus after 12 months
Second-order fractional polynomial P1=0, P2=1	32.77	✓	78%	Plateaus after 12 months

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
P1=1 (Gompertz)	31.76	✓✓	72%	Plateaus after 24 months
Second-order fractional polynomial P1=1, P2=-1	32.21	✓	78%	Plateaus after 24 months
Second-order fractional polynomial P1=1, P2=-0.5	32.37	✓	78%	Plateaus after 12 months
Second-order fractional polynomial P1=1, P2=0	32.79	✓	78%	Plateaus after 12 months
Second-order fractional polynomial P1=1, P2=0.5	33.04	✗	78%	Plateaus after 12 months
Second-order fractional polynomial P1=1, P2=1	33.12	✗	78%	Plateaus after 12 months
Log-normal	31.51	✓✓	51%	Decreases over time
Log-logistic	32.75	✓	45%	Decreases over time

It is also worth noting that for extrapolations based on the observed cemiplimab data, experts' opinion was formally elicited to determine the long-term survival associated with cemiplimab. Experts recruited for this part of the exercise were required to have treatment experience with cemiplimab. The study was double-blind, meaning neither the experts nor the study sponsor was identified to each other. Nine experts participated in the cemiplimab elicitation exercise. The estimates obtained from the formal expert elicitation were combined with the empirical trial data using fractional polynomial models to determine which distributions provided the most credible extrapolated survival curves. Information elicited from each expert regarding the survival proportions and related uncertainties at each time point were integrated using a normal distribution. The evidence synthesis methods and results from the expert elicitation study are described in detail in Appendix M.

Given that clinical experts who participated in this part of the elicitation exercise were investigators of the Phase II EMPOWER-CSCC 1 trial, survival estimates were only elicited based on trial data from the Phase II trial by estimating the upper and lower plausible limits and the most likely value of survival at 2, 3, 4 and 5 years. Similar estimates are not available for the integrated analysis of the Phase II and Phase I trials which forms the base case of this submission. Therefore, in the base case, results from the elicitation exercise for cemiplimab were only used to visually and indirectly compare the extrapolated curves described above with the experts' estimates. When the long-term survival estimates from the extrapolated curves were compared with experts' long-term survival estimates based on the Phase II trial data (Figure 26), it appeared that long term survival estimates derived from the extrapolations in the base case are more conservative than those based on the experts' elicitation. A scenario analysis utilising the results for both chemotherapy and cemiplimab from the expert elicitation exercise is provided in Section B.3.8.3.

Figure 26: Expected outcomes based on best fitting model with and without expert information for cemiplimab from the Phase II, EMPOWER-CSCC 1 trial



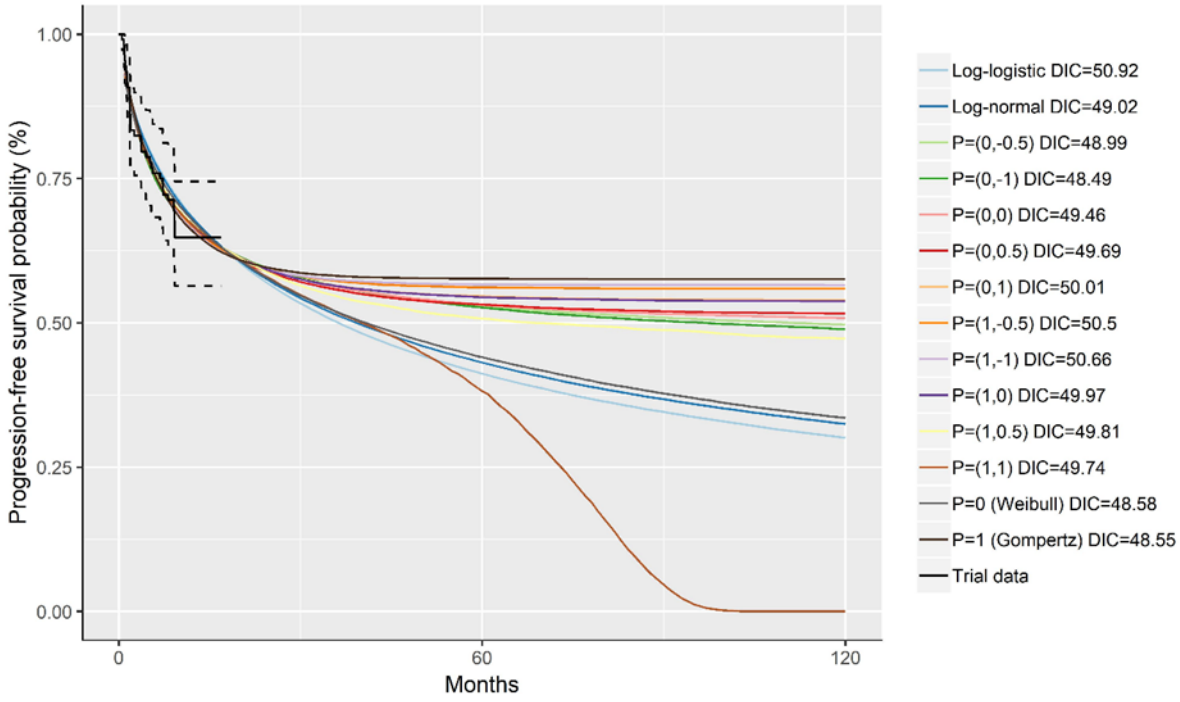
B.3.3.2.4. Progression-free and overall survival for cemiplimab based on population adjusted results from the simulated treatment comparisons (used in scenario analyses)

Figure 27 and Figure 28 summarise the estimated PFS and OS based on the alternative parametric distributions fitted to the adjusted cemiplimab curves, given the target population from Jarkowski 2016, and include the DIC for each distribution. The goodness of fit and plausibility of alternative parametric distributions to extrapolate PFS and OS with cemiplimab are summarised in Table 21 and Table 22, respectively.

Best-fitting distributions were considered to be the ones with the lowest DIC values that also declined over time, which were Weibull for PFS and Gompertz for OS. Distributions that declined over time were preferred for cemiplimab over curves that plateaued in the long-term because the observed data is limited and therefore this approach was deemed to be more conservative. However, when plausibility of the

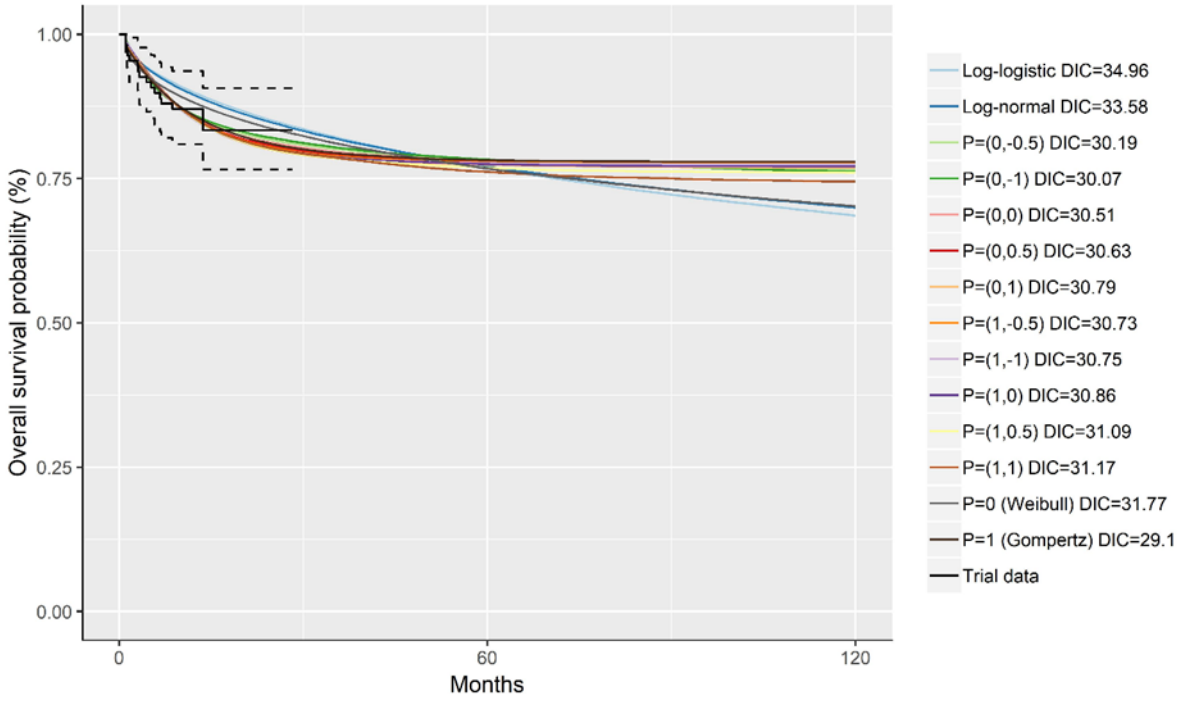
survival extrapolations based on the 'predicted' cemiplimab data was considered, all of the fitted parametric distributions produced long-term survival estimates that appeared to lack clinical validity, given the currently limited available data, with OS values of 75% to 79% at 60 months. When comparing the results of these distributions with the ones fitted for the naïve comparison, the fitted curves for the naïve comparison produced lower long-term estimates (with OS and PFS values of 51% and 21% at 60 months respectively). Thus, the naïve comparison was used for the base case as this resulted in more credible survival estimates given the currently immature cemiplimab data. However, cost-effectiveness results based on the efficacy extrapolations from the STC are presented as a scenario analysis.

Figure 27: Progression-free survival curves for cemiplimab based on simulated treatment comparisons model matching Jarkowski 2016



Key: DIC, deviance information criterion.

Figure 28: Overall survival curves for cemiplimab based on simulated treatment comparisons model matching Jarkowski 2016



Key: DIC, deviance information criterion.

Table 21: Goodness of fit and plausibility of alternative parametric distributions used to estimate PFS curves for cemiplimab with STC

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	PFS at 60 months	Extrapolation
Weibull (P1=0)	48.58	✓✓	44%	Decreases over time
Second-order fractional polynomial P1=0, P2=-1	48.49	✓✓	53%	Plateaus at 60 months
Second-order fractional polynomial P1=0, P2=-0.5	48.99	✓✓	53%	Plateaus at 72 months
Second-order fractional polynomial P1=0, P2=0	49.46	✓	53%	Plateaus at 60 months
Second-order fractional polynomial P1=0, P2=0.5	49.69	✓	53%	Plateaus at 48 months

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	PFS at 60 months	Extrapolation
Second-order fractional polynomial P1=0, P2=1	50.01	✗	55%	Plateaus at 36 months
P1=1 (Gompertz)	48.55	✓✓	58%	Plateaus at 24 months
Second-order fractional polynomial P1=1, P2=-1	50.66	✗	57%	Plateaus at 36 months
Second-order fractional polynomial P1=1, P2=-0.5	50.50	✗	56%	Plateaus at 36 months
Second-order fractional polynomial P1=1, P2=0	49.97	✓	55%	Plateaus at 36 months
Second-order fractional polynomial P1=1, P2=0.5	49.81	✓	51%	Plateaus at 60 months
Second-order fractional polynomial P1=1, P2=1	49.74	✓	38%	Decreases over time
Log-normal	49.02	✓	43%	Decreases over time
Log-logistic	50.92	✗	41%	Decreases over time

Table 22: Goodness of fit and plausibility of alternative parametric distributions used to estimate OS curves for cemiplimab with STC

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
Weibull (P1=0)	31.77	✓	78%	Decreases over time, general mortality >60 months
Second-order fractional polynomial P1=0, P2=-1	30.07	✓✓	78%	Decreases over time, general mortality >35 months
Second-order fractional polynomial P1=0, P2=-0.5	30.19	✓✓	78%	Decreases over time, general mortality >35 months

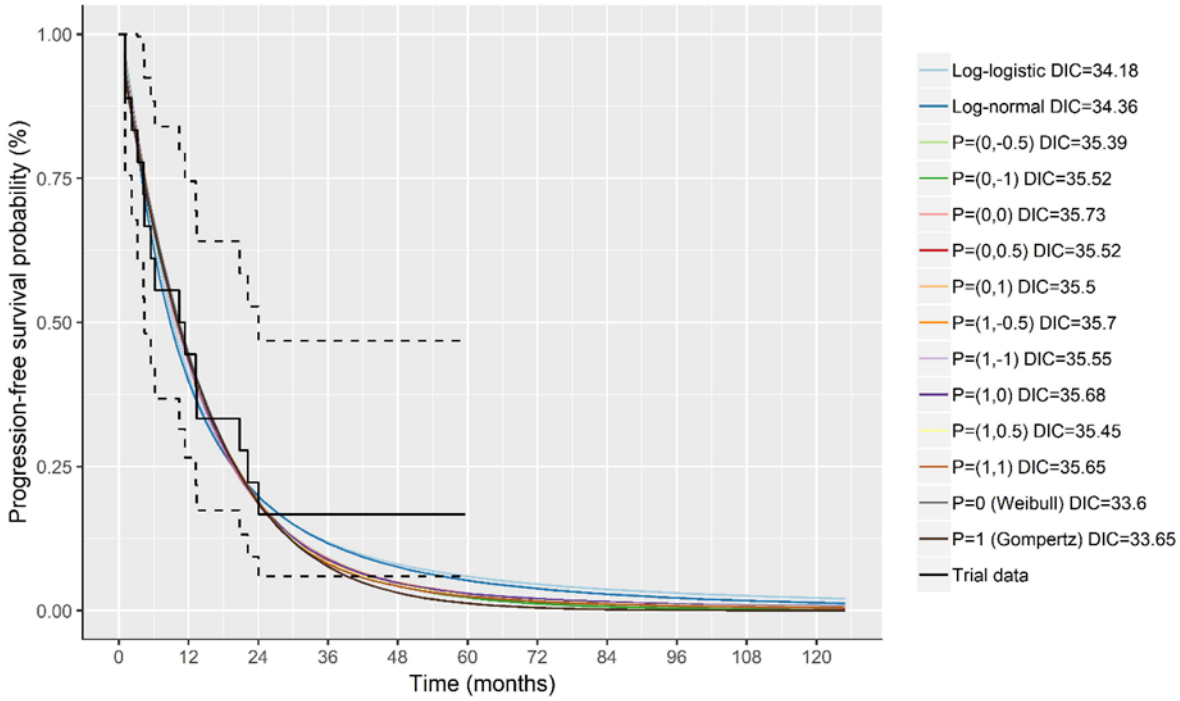
Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
Second-order fractional polynomial P1=0, P2=0	30.51	✓✓	78%	Decreases over time, general mortality >33 months
Second-order fractional polynomial P1=0, P2=0.5	30.63	✓✓	78%	Decreases over time, general mortality >33 months
Second-order fractional polynomial P1=0, P2=1	30.79	✓✓	77%	Decreases over time, general mortality >32 months
P1=1 (Gompertz)	29.10	✓✓✓	78%	Decreases over time, general mortality >31 months
Second-order fractional polynomial P1=1, P2=-1	30.75	✓✓	78%	Decreases over time, general mortality >31 months
Second-order fractional polynomial P1=1, P2=-0.5	30.73	✓✓	78%	Decreases over time, general mortality >31 months
Second-order fractional polynomial P1=1, P2=0	30.86	✓✓	77%	Decreases over time, general mortality >31 months
Second-order fractional polynomial P1=1, P2=0.5	31.09	✓	77%	Decreases over time, general mortality >32 months
Second-order fractional polynomial P1=1, P2=1	31.17	✓	76%	Decreases over time, general mortality >34 months
Log-normal	33.58	✗✗	77%	Decreases over time, general mortality >60 months
Log-logistic	34.96	✗✗	77%	Decreases over time, general mortality >60 months

B.3.3.2.5. Progression-free and overall survival for chemotherapy

Figure 29 and Figure 30 summarise the estimated PFS and OS based on the alternative parametric distributions fit to the observed chemotherapy data and include the DIC for each distribution. The goodness of fit and plausibility of alternative parametric distributions to extrapolate PFS and OS with chemotherapy are summarised in Table 23 and Table 24, respectively.

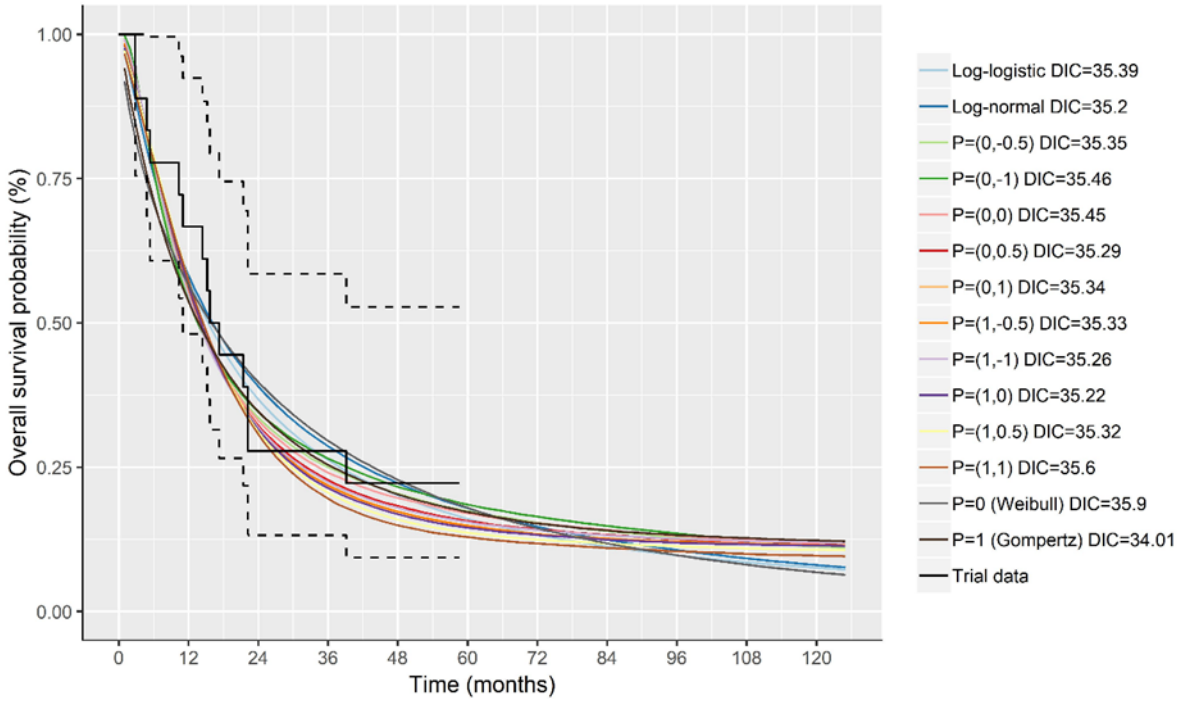
Best-fitting distributions were considered to be the ones with the lowest DIC values, Gompertz for OS and Weibull for PFS. In the scenario analyses, Lognormal or Log-logistic and Lognormal or second-order fractional polynomial with P1=1 and P2=0 functions were explored for PFS and OS, respectively.

Figure 29: Progression-free survival curves for chemotherapy estimated using alternative parametric models based on analysis of patients who received chemotherapy



Key: DIC, deviance information criterion.

Figure 30: Overall survival curves for chemotherapy estimated using alternative parametric models based on analysis of patients who received chemotherapy



Key: DIC, deviance information criterion.

Table 23: Goodness of fit and plausibility of alternative parametric distributions used to estimate progression-free survival curves with chemotherapy

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	PFS at 60 months	Extrapolation
Weibull (P1=0)	33.60	✓✓	1%	Decreases over time
Second-order fractional polynomial P1=0, P2=-1	35.52	✗	2%	Decreases over time
Second-order fractional polynomial P1=0, P2=-0.5	35.39	✗	3%	Decreases over time
Second-order fractional polynomial P1=0, P2=0	35.73	✗	3%	Decreases over time

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	PFS at 60 months	Extrapolation
Second-order fractional polynomial P1=0, P2=0.5	35.52	✗	3%	Decreases over time
Second-order fractional polynomial P1=0, P2=1	35.50	✗	3%	Plateaus at 72 months
P1=1 (Gompertz)	33.65	✓✓	1%	Decreases over time
Second-order fractional polynomial P1=1, P2=-1	35.55	✗	3%	Plateaus at 96 months
Second-order fractional polynomial P1=1, P2=-0.5	35.70	✗	3%	Plateaus at 96 months
Second-order fractional polynomial P1=1, P2=0	35.68	✗	3%	Plateaus at 96 months
Second-order fractional polynomial P1=1, P2=0.5	35.45	✗	3%	Plateaus at 84 months
Second-order fractional polynomial P1=1, P2=1	35.65	✗	3%	Plateaus at 84 months
Log-normal	34.36	✓	5%	Decreases over time
Log-logistic	34.18	✓	6%	Decreases over time

Table 24: Goodness of fit and plausibility of alternative parametric distributions used to estimate overall survival curves with chemotherapy

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
Weibull (P1-0)	35.90	✓	18%	Decreases over time
Second-order fractional polynomial P1=0, P2=-1	35.46	✓	19%	Decreases over time
Second-order fractional polynomial P1=0, P2=-0.5	35.35	✓	17%	Decreases over time

Model	Goodness of fit to data (up to 16 months)		Clinical and epidemiological plausibility of extrapolation (>16 months)	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
Second-order fractional polynomial P1=0, P2=0	35.45	✓	17%	Plateaus at 84 months
Second-order fractional polynomial P1=0, P2=0.5	35.29	✓	16%	Plateaus at 72 months
Second-order fractional polynomial P1=0, P2=1	35.34	✓	15%	Plateaus at 72 months
P1=1 (Gompertz)	34.01	✓✓	17%	Plateaus at 84 months
Second-order fractional polynomial P1=1, P2=-1	35.26	✓	16%	Plateaus at 72 months
Second-order fractional polynomial P1=1, P2=-0.5	35.33	✓	15%	Plateaus at 84 months
Second-order fractional polynomial P1=1, P2=0	35.22	✓	15%	Plateaus at 72 months
Second-order fractional polynomial P1=1, P2=0.5	35.32	✓	14%	Plateaus at 72 months
Second-order fractional polynomial P1=1, P2=1	35.60	✓	13%	Plateaus at 72 months
Log-normal	35.20	✓	18%	Decreases over time
Log-logistic	35.39	✓	16%	Decreases over time

As with the extrapolations for cemiplimab based on the observed data, experts' opinion was formally elicited to determine the long-term survival associated with chemotherapy. The SHELF was used to elicit the opinion of experts on what they expected long-term survival to be with chemotherapy. Six experts participated in the chemotherapy elicitation exercise. The estimates obtained were combined with published data from the Jarkowski 2016[6] study to determine which distributions provided the most credible extrapolated survival curves. The evidence synthesis methods and results from the expert elicitation study are described in detail in Appendix M.

When the Jarkowski 2016[6] trial data was modelled in combination with the expert elicited OS and PFS proportions (6, 7, 8, 9 and 10 years), the DIC suggested that the Log normal and Gompertz distributions were the best-fitting models for OS and PFS, respectively. The expert information presented in Figure 32 reduced the uncertainty in the parameter estimates slightly as compared to the model without any expert information. The expected OS that incorporated expert information was less than the expected OS without expert information. In the context of PFS as presented in Figure 31, the uncertainty was not reduced and the point estimates were higher when including expert information compared with the model without expert information. Given the remaining uncertainty associated with the experts' elicitation estimates, and to be consistent with the approach followed in the base case for the extrapolations of the cemiplimab efficacy, in the base case analyses experts' estimates were not taken into account for chemotherapy extrapolations. A scenario analysis is explored, however, where the long-term survival estimates are based on the experts' elicitations for both cemiplimab and chemotherapy.

Figure 31: Modelled PFS over time assuming Gompertz distribution based on observed data from Jarkowski 2016 (5 years) for platinum chemotherapy combined with OS at 6, 7, 8, 9, and 10 years based on expert elicitations

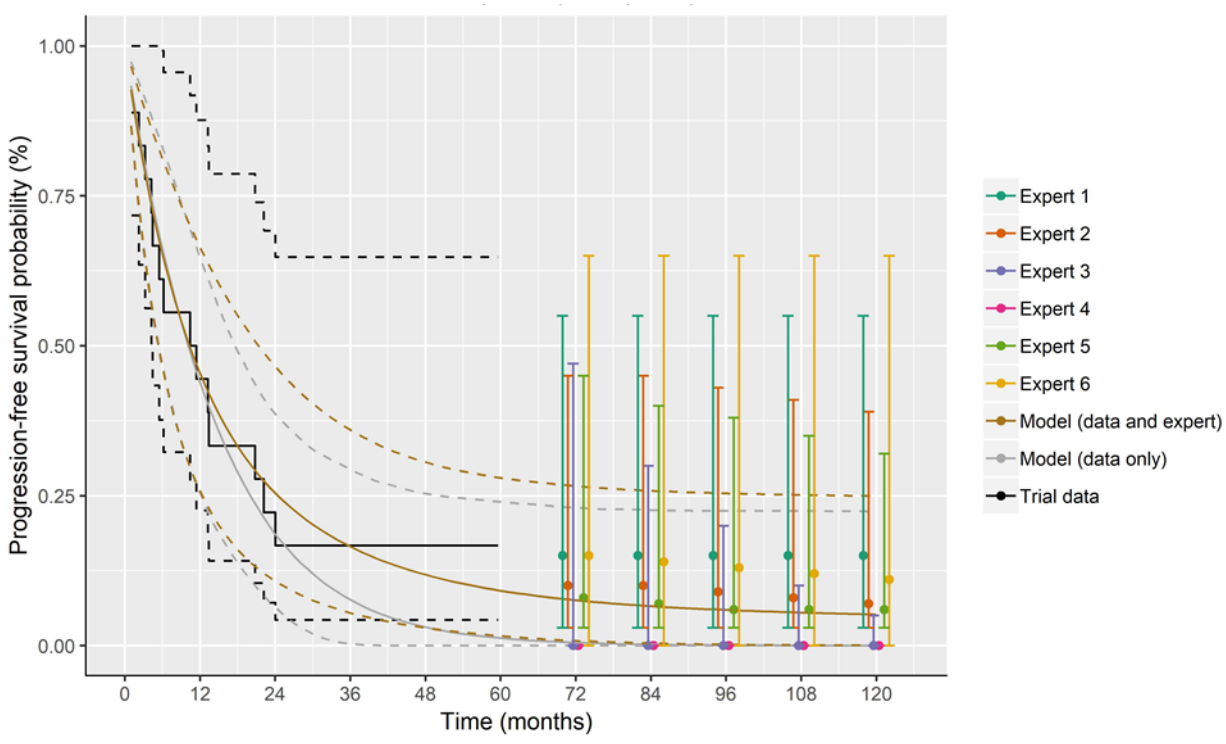
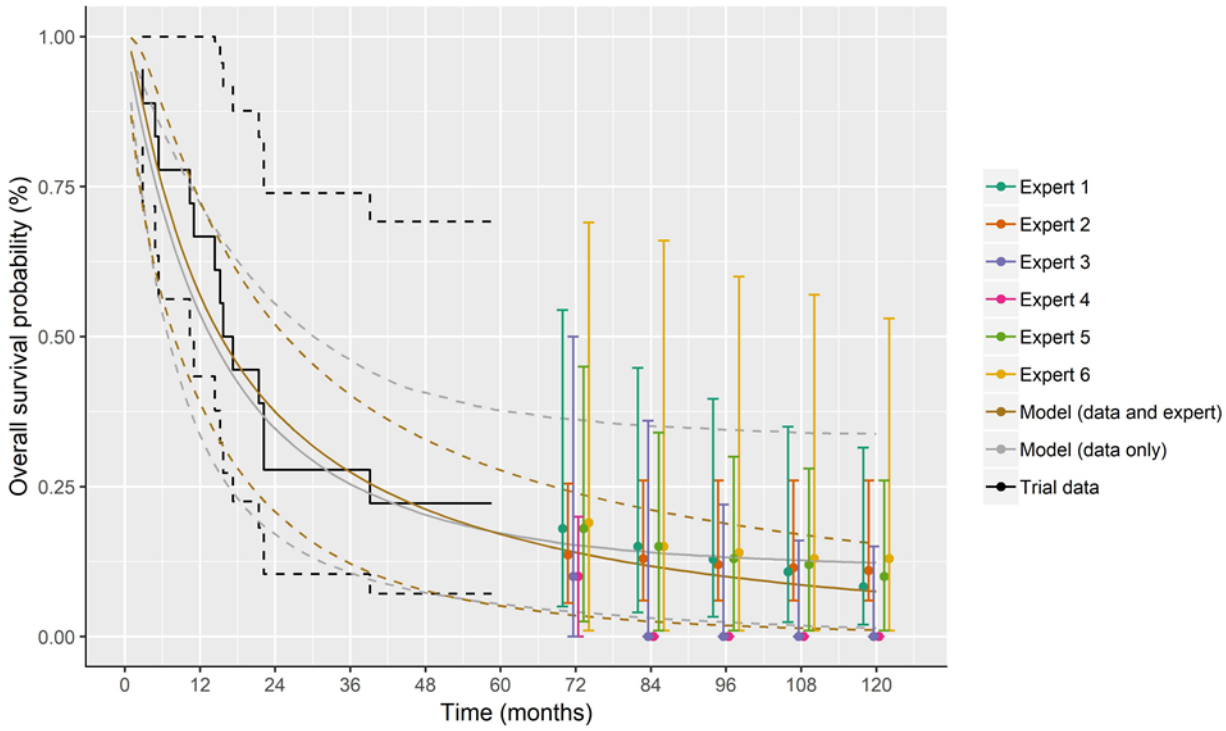


Figure 32: Modelled survival over time assuming Gompertz distribution based on observed data from Jarkowski 2016 (5 years) for platinum chemotherapy combined with OS at 6, 7, 8, 9 and 10 years based on expert elicitations



B.3.3.2.6. Progression-free survival and overall survival for best supportive care

As discussed in Section B.3.2.3, no data for BSC were identified. Given this paucity of data relating to the use of palliative care in advanced CSCC, in the base case an assumption was made to use the same extrapolated OS and PFS curves based on the chemotherapy observed data as described in Section B.3.3.2.5. This was considered to be a conservative assumption.

However, given the uncertainty surrounding these estimates alternative scenario analyses were conducted using broad results from the efficacy and safety SLR in CSCC. This SLR identified data for a number of epidermal growth factor receptor (EGFR) inhibitors (for example cetuximab, gefitinib and erlotinib) which are not licenced or reimbursed in the UK but that market research suggests are occasionally used off-label. Therefore, in this analysis, the EGFR studies identified through the SLR were pooled together to create proxy efficacy estimates for BSC on the basis that clinical opinion, sought at an advisory board, suggested EGFRs were not

expected to be effective in CSCC. In addition, a scenario analysis was explored were all studies identified in this SLR including EGFR and the Jarkowski 2016 study were naively pooled together to create an alternative proxy for BSC. Alternative parametric distributions were fit to this pooled data in each scenario as explained in detail in Appendix P.

All of the above approaches were discussed at a UK advisory board held by Sanofi, with both clinical and health economic experts (three clinical oncologists and two health economists attended the meeting). Clinical experts considered these reasonable approaches in the absence of more robust evidence for BSC.

Sanofi is currently conducting a retrospective chart review study, aimed at gaining a better understanding of the current management and outcomes of advanced CSCC by collecting data from approximately an estimated number of 600 patients in the US and EU, as discussed in Section B.2.11. When this study reports in 2019, it is anticipated it will help reduce some of the uncertainty around the efficacy associated with the current standard of care.

B.3.3.3. Treatment duration

B.3.3.3.1. Cemiplimab: treatment duration and stopping rule

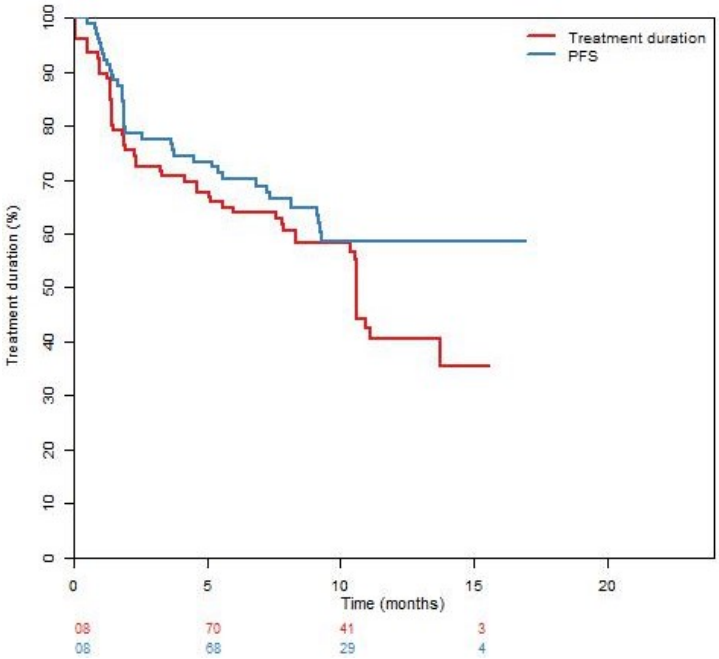
The model assumes the duration of therapy with cemiplimab is equal to the time spent in the pre-progression health state, in line with the Phase II trial design and the anticipated SmPC. This assumption was made on the basis of an assessment of the relationship between PFS and time on treatment and is applied until the treatment effect of cemiplimab stops following a cap of 22 months as described below.

This assessment of the relationship between PFS and time on treatment was undertaken given that historic evidence in immuno-oncology has previously shown the observed time on treatment may differ from PFS. To this end, the relationship between PFS and time to end treatment was compared based on data from the integrated analysis of the cemiplimab trials.

The results from this analysis showed a difference between the PFS and time to end of treatment. Integrated analysis data shows a sharp decrease in the number of

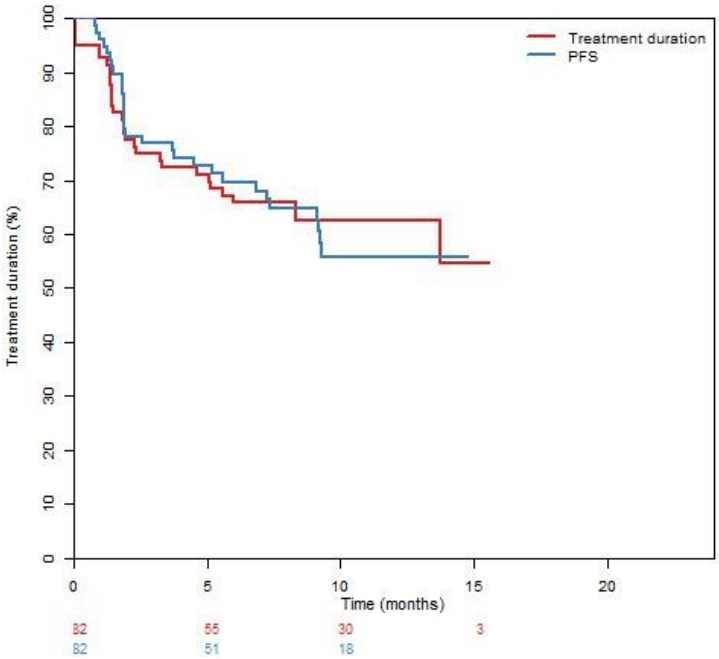
patients being treated at around 10 months (Figure 33). This is due to the implementation of an artificial treatment cap in the Phase I trial whereby patients do not continue treatment beyond 48 weeks. Since this stopping rule was not used for the Phase II EMPOWER-CSCC 1, and is not in line with clinical experts' expectation on how cemiplimab would be used in a clinical setting, treatment duration based on only the Phase II EMPOWER-CSCC 1 trial was deemed to provide a better representation of the relationship between PFS and treatment duration. Therefore, further assessment of this relationship based on just the Phase II EMPOWER-CSCC 1 trial is presented in Figure 34. As can be seen, there are only small and not statistically significant (HR: 0.956 [95% CI: 0.575, 1.588]) differences between PFS and the time to end treatment in the Phase II EMPOWER-CSCC 1 data. Therefore, it was regarded appropriate for the base case to assume that duration of therapy with cemiplimab is equal to the time spent in the pre-progression health state. However, despite the minor differences, to ensure the model was sufficiently flexible an adjustment was included to PFS of a HR 0.956 (95% CI: 0.575, 1.588), based on the difference between PFS and treatment duration to implement. This was used to estimate the treatment duration in the cemiplimab arm in a scenario analysis.

Figure 33: Assessment of the progression-free survival versus the time to end of treatment based on the integrated analysis of the cemiplimab trials



Key: PFS, progression-free survival.

Figure 34: Assessment of the PFS versus the time to end of treatment based on the Phase II EMPOWER CSCC-1 cemiplimab trial



Key: PFS, progression-free survival.

NICE appraisals for other immunotherapies in the same class as cemiplimab have given consideration to stopping treatment after a defined period of time (2 years).[68, 71-78] Optimal treatment duration for immunotherapies is uncertain and an ongoing area of research. Given the cemiplimab phase II study specifies that patients are treated until progression, unacceptable toxicity or 96 weeks (22 months) the base case economic analysis incorporates a 22 month stopping rule. Implementation of a 24 month (2 year) stopping rule is provided as a sensitivity analysis given that this rule is in place for other immunotherapies. As discussed in NICE TA520 there are growing clinical concerns about using immunotherapies beyond 2 years.[68] Indeed clinicians consulted regarding this submission felt that a stopping rule was appropriate and that in reality they would expect very few patients to still be on treatment at 2 years. Furthermore, in other immunotherapy appraisals the CDF clinical lead has stated that a 2-year stopping rule is acceptable to both patients and clinicians and is implementable.[68, 73, 74, 76-78]

B.3.3.3.2. The cemiplimab long-term treatment effect following application of the 22-month stopping rule

In the base case analyses, the best fitting distributions, as described in Section B.3.3.2.3, were used to extrapolate the cemiplimab hazard up to 22 months. There is now compelling evidence that patients' continue to respond to PD-1 treatments after treatment discontinuation.[13, 14] However, the duration of this continued benefit is currently uncertain. Indeed previous NICE appraisals have accepted that given the mechanism of action of this class of treatments a continued treatment benefit is clinically plausible.[68, 71-75, 78]

Sanofi have therefore considered a range of analyses where continued benefits are capped at different time points (22 months, 3 years, 5 years, lifetime) consistent with the approach followed in other appraisals.[68, 71-75, 78] In the base case the treatment effect of cemiplimab is assumed to last for up to 3 years as this leads to conservative, clinically plausible long term survival estimates. Following 3 years of extrapolation, the hazard was then set equal to the hazard rate associated with chemotherapy. As this is a key area of uncertainty for this appraisal additional scenarios are also explored. These scenario analyses include capping the cemiplimab treatment effect at different time points (at 22 months or 5 years), applying a waning effect or a constant hazard beyond the 22 months and a scenario based on clinical experts' opinion where the results of a formal expert elicitation exercise are used to inform long term survival estimates for both cemiplimab and chemotherapy treatment arms.

B.3.3.3.3. Chemotherapy and best supportive care: treatment duration

Chemotherapy is assumed to be administered for a maximum of 6 treatment cycles. This assumption is consistent both with the clinical practice in the UK and assumptions made in previous NICE appraisals.[64, 73] Feedback from clinical experts suggested that many patients would not receive 6 cycles of chemotherapy due to the associated toxicity. Therefore a scenario analysis assuming patients only receive 3 cycles is also provided.

In terms of BSC, an explicit treatment duration assumption was not made as BSC did not consist of any active treatment. Therefore, any palliative care costs and resource use implications were assumed to apply throughout the duration of receipt of palliative care until the end of life.

B.3.3.4. Adverse events

For the cemiplimab arm, rates of Grade 3 and 4 AEs were included as these AEs were considered to incur higher costs and have greater impact on QoL and were based on data from the Phase I and Phase II EMPOWER-CSCC 1 cemiplimab trials (Table 25). The proportion of patients with AEs were pooled using inverse weighted variance. AEs included in the model were only those experienced by patients receiving a weighted dose of cemiplimab. Patients receiving a flat dose (Group 3, Phase II EMPOWER-CSCC 1) have been excluded to remain consistent with the absence of efficacy data for patients receiving a flat dose at the point of this submission.

Table 25: Adverse event rates applied for cemiplimab

Adverse event	Point estimate	Standard error
Skin infection	1.1%	0.01
Hypercalcaemia	2.1%	0.01
Failure to thrive	7.7%	0.05
Fatigue	1.8%	0.01
Hypokalaemia	1.8%	0.01
Anaemia	0.9%	0.01
Source: Sanofi data on file, 2018[44]		

Since there is no connected network of RCTs available to estimate the relative effect (that is odds ratios), estimates for the Grade 3 or 4 AEs for chemotherapy were based on the unadjusted estimates of AEs from the published literature. There were no AEs reported in the Jarkowski *et al*. (2016) study for chemotherapy.[6] In addition, no other studies were identified investigating platinum based chemotherapy in CSCC patients that reported AEs (see Section B.2.1). Therefore, the rate of AEs were sourced from the control arm of the Vermorken *et al*. (2013) trial,[79] investigating cisplatin and fluorouracil with or without panitumumab in patients with recurrent or

metastatic squamous cell carcinoma of head and neck (SCCHN). The study was identified through a targeted literature review and considered the most appropriate given the absence of CSCC specific data as validated by clinical experts who had suggested that SCCHN would be the closest tumour type to borrow data from.

A comparison of the baseline characteristics between the control arm of the Vermorken *et al*. (2013)[79] trial and the Phase II EMPOWER-CSCC 1 study[45] showed the trials to be broadly comparable, with the proportion of males enrolled being 87% and 85.4%, respectively. However, it is of note the Vermorken *et al*. (2013) trial included younger patients (average age of 59 years old versus 70.5 years old) and the ECOG was generally poorer (69% of patients with ECOG of 1 versus 54.7% in the Phase II EMPOWER-CSCC 1 study). Despite similarities, such differences are expected between the CSCC and SCCHN populations; Vermorken *et al*. (2013) was considered to be the best available source for AEs specific to the administration of platinum based chemotherapy.

Table 26 presents AE rates used in the economic model for chemotherapy as identified in the Vermorken *et al*. (2013) study.

Table 26: Adverse event rates applied for chemotherapy

Adverse event	Point estimate	Standard error
Hypokalaemia	7.1%	0.01
Stomatitis or oral mucositis	8.6%	0.02
Neutropenia	32.6%	0.03
Anaemia	14.5%	0.02
Thrombocytopenia	7.7%	0.02
Febrile neutropenia	5.2%	0.01
Source: Vermorken et al. 2013.[79]		

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life studies

An SLR was initially conducted in October 2017 to identify relevant HRQL data for adults with advanced CSCC. Searches were rerun in September 2018 with no additional studies of relevance to the decision problem identified. Details from the

SLR, including the search terms, eligibility criteria and the PRISMA diagram are presented in Appendix H.

The SLR identified 355 records for HRQL studies. Of those, no relevant HRQL studies were identified.

B.3.4.2. Health-related quality of life data from clinical trials

The impact of cemiplimab on QoL was assessed in the Phase II EMPOWER-CSCC 1 study using EORTC QLQ-C30.[45] QoL data was not captured in the Phase I cemiplimab study and therefore only data from the Phase II study was available for the needs of the cost-effectiveness analyses.

In detail, the global health status/QoL, 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain and nausea and vomiting), a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea), and perceived financial impact of the disease was computed using the EORTC QLQ-C30 scoring procedures.[80] The QoL of patients was repeatedly measured by the EORTC QLQ-C30 at Day 1 of each treatment cycle. The change scores of EORTC QLQ-C30 were summarised descriptively at each post baseline time point (see Section B.2.6.4).

In the NICE reference case, EQ-5D-3L is the preferred instrument to measure and express utility in cost-effectiveness analyses.[63] Therefore, a mapping exercise was undertaken to convert the EORTC QLQ-C30 values captured in the Phase II EMPOWER-CSCC 1 study to EQ-5D values as described below. EORTC QLQ-C30 has previously been shown to reliably and validly measure the QoL of patients with NMSC, although it may not be as sensitive to specific NMSC aspects of QoL.[81]

B.3.4.3. Mapping

To estimate the utility pre- and post-progression for patients with advanced CSCC expressed in EQ-5D values, it was necessary to map the scores from EORTC QLQ-C30 from the EMPOWER-CSCC 1 to EQ-5D patient preferences using IPD from EMPOWER-CSCC 1. Full details of the mapping methods and results are presented in Appendix N.

Identification of mapping algorithms

In summary, in order to identify appropriate mapping algorithms, a literature search was conducted with a three-step process. Firstly, the Health Economics Research Centre (HERC) database of mapping studies was searched to identify all studies that mapped EORTC QLQ-C30 to EQ-5D. The second step was a targeted search, conducted in PubMed, to identify publications that fell outside of the time period covered by the HERC database. The third approach consisted of a search of all NICE technical appraisals to provide context regarding the suitability of mapping algorithms.

The literature search identified 135 studies contained in the HERC database and 17 publications from the PubMed search. These publications provided information on 11 unique algorithms for mapping EORTC QLQ-C30 values to EQ-5D in cancer patients. Nine of the algorithms were based on linear regression methods, one was based on a mixed model and one was based on multinomial response mapping. Two review articles were also identified which compared the predictive qualities of most of these algorithms. The review articles obtained external validation datasets with both EORTC QLQ-C30 and EQ-5D values and compared mapping to observed EQ-5D values. Forty oncology related submissions were identified in the search of technical appraisals. Four of these used a mapping algorithm to obtain EQ-5D values from EORTC QLQ-C30 data.

Mapping algorithm used in the base case

Out of the identified mapping algorithms, the Longworth et al algorithm[82] was selected to be the mapping algorithm for this analysis because of its past predictive ability, and similarities to the current population of interest in Phase II EMPOWER-CSCC 1. In addition, this algorithm differs from the other ones examined in that it uses response mapping rather than a simple linear model to predict the EQ-5D. This approach uses the values of the EORTC dimensions to predict the probability of an individual being in one of the 243 possible EQ-5D states, and then applies the specific tariffs to these probabilities to obtain the EQ-5D score.

Comparison of EMPOWER-CSCC 1 versus mapping algorithms

Moreover, it is worth noting the selection of the most appropriate algorithm was complicated because none of the identified algorithms related specifically to cemiplimab or to a population of advanced CSCC. In line with recommendations for the use of mapping algorithms by Wailoo *et al*. (2017),[83] the Phase II EMPOWER-CSCC 1 characteristics were compared with the populations from the estimation datasets for the three algorithms initially selected based on the literature. In general, patients in the Phase II EMPOWER-CSCC 1 appeared to be reasonably similar to those used in the mapping studies. However, some differences were identified between the Phase II EMPOWER-CSCC 1 patients and those patients in the Longworth mapping, such as more males in Phase II EMPOWER-CSCC 1 and possibly less severe patients based on disease stage and ECOG restrictions. However, the comparisons were somewhat limited by the reported information in the publications.

Comparison of the EORTC values also suggested the QoL was slightly better in the Phase II EMPOWER-CSCC 1 compared with the Longworth population. However, the external dataset used in Doble and Lorgelly (2016),[84] one of the identified review articles, also consisted of healthier patients; it was shown that the algorithms still predicted the EQ-5D well. Additionally, both review articles noted that poor estimation occurred more frequently at low health states and good health tended to be estimated well. Given the summary articles found that mapping algorithms were reasonably robust to differences in cancer types, it was reasonable to assume that the observed differences would not lead to large differences, particularly because patients in EMPOWER-CSCC 1 appeared to be reasonably similar to those used in the mapping studies.

Mapping EMPOWER-CSCC 1 EORTC QLQ-30 to EQ-5D

Patient reported EORTC data from the EMPOWER-CSCC 1 was used as inputs into the Longworth algorithm; the resulting mapped EQ-5D data were summarised using descriptive statistics at baseline and by best response status (based on independent assessment) in terms of the mean and standard deviation of the distribution. EQ-5D utilities were summarised for the following health states in terms of the value and

standard error in base case and sensitivity analyses: pre-progression, post-progression, objective response pre-progression and post-progression. The mapping exercise was conducted using the UK tariff. Sensitivity analyses were conducted in which the McKenzie algorithm was used with the UK tariff.[85]

Results of the mapping exercise

Values of EQ-5D were obtained for 62 patients from Phase II EMPOWER-CSCC 1 via the Longworth mapping algorithm, their distributions were summarised at baseline and at the time of tumour assessment. Baseline utilities were highly skewed, ranging from 0 to 0.95, with 75% of the observations falling in the 0.67 to 0.95 range. The median utility at baseline was 0.785. The median utility increased after treatment and the distribution of values was similarly skewed. For progressors, baseline median utility was 0.773, which decreased to 0.606 after progression. Median utility for patients that did not progress increased from 0.785 to 0.886. Utilities were also modelled statistically with a random effects model that allows for subject specific slopes and intercepts and a term for tumour response; these models showed similar trends. Sensitivity analyses using the McKenzie algorithm showed that utilities were consistently estimated regardless of algorithm used.[85]

B.3.4.4. Adverse reactions

Disutility due to Grade 3 and 4 AEs was incorporated in the model in the pre-progression health state as these AEs were considered to incur higher costs and have greater impact on QoL. These utility decrements were derived from previous NICE technology appraisals (TAs) as presented in Table 27. The loss of QALYs per AE was calculated as the product of the utility decrement and the assumed duration of the AE. All AEs were assumed to last for 30 days in the economic model. The loss of QALYs as applied in the cost-effectiveness model is reported in Table 28.

Table 27: Adverse event decrements included in the model

Adverse event	Mean	SE	Source
Skin infection	0.120	0.005	Assumed to be the same as cellulitis, in NICE TA410.[86]
Hypercalcaemia	0.090	0.015	Assumed to be the same as hyponatremia in NICE TA517.[64]

Adverse event	Mean	SE	Source
Failure to thrive	0.073	0.018	Assumed to be same as fatigue. TA490.[73]
Fatigue	0.073	0.018	Assumed to be same as fatigue, in NICE TA490.[73]
Hypokalaemia	0.090	0.015	Assumed to be the same as hyponatremia in NICE TA517.[64]
Stomatitis or oral mucositis	0.151	0.036	Assumed to be same as stomatitis in Lloyd (2006)[87]
Neutropenia	0.090	0.015	Assumed to be same as neutropenia in NICE TA517[64]
Anaemia	0.073	0.018	Assumed to be same anaemia in NICE TA517.[64]
Thrombocytopenia	0.108	0.010	Assumed to be same as thrombocytopenia, Tolley (2013)[88]
Febrile neutropenia	0.090	0.016	Assumed to be same as febrile Neutropenia in NICE TA517[64]
Key: NICE, National Institute of Health and Care Excellence; TA, Technology Appraisal; SE, standard error.			

Table 28: QALY loss due to adverse events as included in the economic model

Adverse event	Mean	SE
Skin infection	0.010	0.001
Hypercalcaemia	0.007	0.001
Failure to thrive	0.006	0.001
Fatigue	0.006	0.001
Hypokalaemia	0.007	0.001
Stomatitis or oral mucositis	0.013	0.001
Neutropenia	0.007	0.001
Anaemia	0.006	0.001
Thrombocytopenia	0.009	0.001
Febrile neutropenia	0.008	0.001

B.3.4.5. Health-related quality of life data used in the cost-effectiveness analysis

In the base case of the economic model, utilities derived from the Phase II EMPOWER-CSCC 1 study using the EORTC QLQ-C30 were incorporated. Given that QALYs need to be expressed in EQ-5D as per the NICE reference case, the

EORTC QLQ-C30 values were converted to EQ-5D values using the Longworth *et al*. (2014) mapping algorithm.[82] These values were considered to be the most appropriate to be included in the base case since they are derived directly from the largest advanced CSCC patient's cohort to be examined in a trial to date.

Utility estimates derived from the Phase II EMPOWER-CSCC 1 study, from patients treated with cemiplimab and mapped to EQ-5D, were assigned to the pre-progression and post-progression health states for cemiplimab chemotherapy and BSC in the cost-effectiveness model. This was considered to be a conservative assumption as it is feasible cemiplimab may have positive effects on QoL beyond delaying progression.

The utility values used in the base case of the cost-effectiveness analysis are summarised in Table 29.

Table 29: Utility estimates used in the base case cost-effectiveness analysis

Health state	Mean	SE
Longworth et al. (2004) algorithm[82]		
Pre-progression	0.793	0.137
Post-progression	0.701	0.175
Key: SE, standard error.		

An age-adjustment on the utilities was applied in the cost-effectiveness model following a study by Ara and Brazier (2011)[89] in order to account for the decrease in utilities as a result of age. Preference-based health-state utility values were estimated based on weights from time trade off valuations from the UK general public[90] and the following model was derived using ordinary least square regression for baseline utility given gender and age:

EQ-5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age -0.0000332 * age ^ 2.

Then a multiplicative model was used, which assumes a proportional effect, to combine the health state of interest (i.e. post-progression) with a multiplier given the baseline utility of the cohort. The multiplier for post-progression (multiplier=0.892) represents the utility of the health state (i.e. utility=0.701 for post-progression)

divided by the baseline utility of patients given the starting age and gender of the utility source (i.e. baseline utility=0.786 based on age of 70.4 years; 85% male from EMPOWER-CSCC 1). This approach was in line with suggestions by the Evidence Review Group in a previous NICE submission in urothelial cancer.[77] For the pre-progression, the multiplier was 1.009 given that the utility for progression-free survival was 0.793 and the baseline utility for the population was 0.786. Consequently, the adjustment for this health state was not applied.

Additionally, sensitivity analyses were performed using the McKenzie *et al*. (2009) mapping algorithm,[85] between EORTC QLQ-C30 to EQ-5D, which was also identified in the literature review of the mapping exercise as having good predictive qualities.

Given the challenge in estimating utilities for the target population, particularly for the post-progression state where sample size is limited, alternative utility estimates source directly from the public domain were incorporated in the economic model as additional sensitivity analyses. These alternative utility estimates were sourced from previous NICE TAs that were initially considered to provide relevant QoL data given the uncertainty described previously. However, when these utilities were discussed with UK clinical experts, they did not recommend using data from other cancer types such as basal cell carcinoma, SCCHN and Merkel cell carcinoma, as the biology, management and outcomes of these cancers differ to CSCC. Therefore, in this context, the alternative utilities presented below and the respective scenario analyses should be treated with caution.

One alternative was based on NICE TA473 for cetuximab in recurrent or metastatic SCCHN[91] and additional published economic evaluations, where utility data was derived from the EXTREME trial using QLQ-C30 global health status scores mapped onto EQ-5D values.[91-93] The same utility information was used as a scenario analysis in the NICE HTA, evaluating nivolumab in the same population (TA490).[73]

Another alternative was based on the NICE TA for vismodegib in BCC, where the SF-36 data in the ERIVANCE trial was mapped to EQ-5D tariff scores, using a mapping algorithm published by Rowen *et al*.,[94] which aligns with the NICE reference case prioritising use of EQ-5D.[63]

A summary of the utility values used for the sensitivity analyses is presented in Table 30.

Table 30: Utility estimates used for sensitivity analysis

Health state	Group	Mean	SE	Description	Source
Alternative scenario using data from HNSCC submissions					
Pre-progression	Response	0.67	-	EXTREME trial[92] EORTC QLQ-C30 data mapped to EQ-5D	Hannouf *et al*.[93] NICE TA473[91]
	SD	0.67	-		
Post-progression	All	0.52	-		
Alternative scenario using data from vismodegib submission for BCC					
Pre-progression	laBCC	0.839	0.014	SF-36 data mapped to EQ-5D	ERIVANCE trial[95, 96]
	mBCC	0.819	0.017		
Post-progression	laBCC	0.757	0.037		
	mBCC	0.639	0.109		
McKenzie et al. (2009) algorithm[85]					
Pre-progression	All	0.815	0.158	EORTC QLQ-C30 data mapped to EQ-5D	Phase II EMPOWER-CSCC 1 trial
Post-progression	All	0.719	0.203		

Key: EORTC, European Organization for Research and Treatment of Cancer; EQ-5D, EuroQol-5D; HNSCC, head and neck squamous cell carcinoma; laBCC, locally advanced basal cell carcinoma (not candidates for surgery); mBCC, metastatic basal cell carcinoma; SD, stable disease; SE, standard error; SF-36, 36-Item Short Form Survey.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

In the economic model only direct healthcare costs were included from an NHS perspective. The costs were stratified in terms of pre-progression and post-progression. Costs related to pre-progression included drug costs (acquisition and administration), monitoring costs associated with routine care and AE costs. Costs related to post-progression included palliative treatment and monitoring that are related to routine care.

An SLR was conducted in July 2018 to identify relevant cost and resource use data for adults with advanced CSCC. Details from the SLR, including the search terms, eligibility criteria and the PRISMA diagram, are presented in Appendix I.

Following the primary screening stage a total of 91 articles were assessed in full for further evaluation. All these studies were excluded as they did not meet the prerequisite inclusion/exclusion criteria. No additional studies were identified from the grey literature search (conference search and HTA website searching). Thus, no relevant study reporting cost and resource use evidence within the UK healthcare setting for advanced CSCC was identified in the review.

Given the limited information available on advanced CSCC patients, also reflected in the resource use and costs SLR, an alternative approach was considered utilising healthcare resource use data from other melanoma or non-melanoma NICE HTA submissions. However, this approach was discounted based on feedback from clinical experts on an advisory board according to which healthcare resource use in advanced CSCC differs considerably compared to other types of skin cancer given the biology, management and outcomes of these cancers.

Based on the feedback from clinical experts, a pragmatic approach was taken for the base case of the cost-effectiveness analysis. In this approach, clinical experts with experience in treating advanced CSCC patients within the NHS were asked to provide their estimates of healthcare resource utilisation associated with the management of patients with advanced CSCC. These estimates were consequently incorporated in the economic model for the pre- and post-progression health states and are presented in detail in Section B.3.5.3.

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Cemiplimab

Cemiplimab is administered as a fixed dose IV infusion of 350mg every three weeks. Patients using cemiplimab are expected to be treated in line with the Phase II trial for a maximum of 96 weeks as discussed in Section B.3.3.3.1.

The list price of the 350mg vial is £[redacted]. A CAA has also been proposed resulting in a price per 350mg vial of £[redacted] and an annual cost of £[redacted]. The CAA price has been used in the base case analyses of this submission. Results based on the list price are also provided alongside these analyses.

In Table 31 the unit cost of cemiplimab, based on both the list and the proposed CAA price, is summarised.

Table 31: Cemiplimab acquisition unit cost based on the indicative list and the proposed CAA price

Dosage, administration	Number of cycles	No of vials	Concentration	Cost per unit based on the list price	Cost per unit based on the proposed CAA discount
350mg cemiplimab administered as an IV infusion over 30 minutes Q3W.[11]	Until progression or treatment cap	1	350mg/7ml	[redacted]	[redacted]
Source: Sanofi data on file.					

With a dosing regimen of 350mg every three weeks, £[redacted] and £[redacted] is also the cost of cemiplimab per treatment cycle based on the list and the proposed CAA price respectively.

B.3.5.1.2. Chemotherapy

Based on UK clinical experts' opinion, a platinum based (mostly cisplatin + 5-fluorouracil) regimen is used in clinical practice for advanced CSCC patients who are fit enough to receive chemotherapy. The unit costs for the treatments comprising the chemotherapy arm in the cost-effectiveness model are summarised in Table 32. The chemotherapy regimen unit costs were sourced from the electronic Market information tool (eMit) (representing the 12-month period to the end of June 2017).[97] Where multiple drug costs were available, the lowest cost per mg was selected. As discussed in Section B.3.3.3.3, chemotherapy is assumed to be administered for a maximum of six treatment cycles. This assumption is consistent both with clinical practice in the UK and assumptions made in previous NICE appraisals.[64, 73] An effort was made to derive dosage regimens for chemotherapy from CSCC specific sources. However, where unavailable, dosage has been sourced from published studies and local prescribing guidelines for the treatment of other NMSCs.

The chemotherapy regimen cost per monthly cycle is summarised in Table 33. In the base case of the economic model, in order to calculate the weight-based chemotherapy costs the mean body surface area (BSA), as reported in the cemiplimab clinical trials, was multiplied by the recommended dosage.

Wastage calculations were included in the base case, based on the inverse of the cumulative normal distribution function for the given BSA distribution. They were derived based on the mean and standard deviation of BSA for each gender in the cemiplimab Phase I and Phase II EMPOWER-CSCC 1 trials.[98] The total drug dosage required for the specific BSA distribution was calculated by multiplying BSA and the recommended drug dosage administration (mg/m^2) for the relevant percentiles of the distribution. The drug wastage was based on the difference between the total recommended dosage and the drug dosage received for chemotherapy, assuming the most efficient use of available vials.

Table 32: Chemotherapy regimen acquisition unit costs

Intervention	Drugs, dosage, administration	Number of cycles	No of vials/ pills	Concentration	Cost per unit (GBP)
Chemotherapy (cisplatin)	100 mg/m^2 cisplatin administered as an intravenous infusion once every 3 weeks[39] or 75mg/m^2 when administered in combination with paclitaxel, once every 3 weeks.	6 cycles[64, 73]	1	10mg/ml	£1.84
				50mg/50ml	£4.48
				100mg/100ml	£10.13
5-FU	1,000mg/m^2 on days 1–4 of a 3-week cycle.[99]	6 cycles[64, 73]	1	500mg/10ml	£1.36
				1,000mg/20ml	£1.29
				2,500mg/100ml	£3.59
				5,000mg/100ml	£7.76
				2,500mg/50ml	£5.16
				5,000mg/20ml, ten vials	£58.3

				1,250mg/10ml, five vials	£21.61
Key: 5-FU, 5-fluorouracil; eMIT, electronic market information tool. **Source:** eMIT 2017.[97]					

Table 33. Chemotherapy regimen costs per monthly cycle

Intervention	Average dosage (mg)	Average wastage (mg)	Share of vial wasted per administration	Cost per administration	Wastage cost per administration	Definition of cycle in days	Administrations per cycle	Acquisition cost per monthly cycle
Estimated using the mean reported weight/BSA in the Phase I and Phase II cemiplimab trials								
Chemotherapy (cisplatin, 100mg/m^2)	194.0	6.0	3.1%	£17.39	£0.54	21	1	£25.96
5-FU	1939.9	60.1	3.1%	£2.50	£0.08	21	4	£14.95

Key: 5-FU, 5-fluorouracil; BSA, body surface area.

B.3.5.1.3. Best supportive care

In the base case, patients receiving BSC were assumed not to incur any additional costs associated with any active treatments based on feedback from the Sanofi advisory board. Only the resource use costs associated with the pre- and post-progression health states, as described in Section B.3.5.3, were assumed to be the costs applied for the BSC arm in the economic model. These costs include palliative RT for a certain proportion of patients eligible to receive the treatment as per the feedback from UK clinical experts. In the base case, 75% of patients in the BSC arm were assumed to receive palliative RT in line with clinical experts' advice both pre- and post-progression.

B.3.5.2. Administration costs and resource use

The cost of drug administration was sourced from the NHS Reference costs.[100] This varies between interventions depending on the expected duration of administration.[101]

Cemiplimab in line with the phase II, EMPOWER CSCC 1 trial and the anticipated licence is administered intravenously at a flat dose of 350mg every three weeks (i.e. 21 days) over 30 minutes. Thus, an administration cost of £173.99 was applied per dose administered as per Table 34 below. The resulting cost applied in the model per model cycle, i.e. 30.4 days, is thus equal to £252.01.

For the cisplatin + 5-FU chemotherapy regimen, it was assumed that the first administration will follow the minimum duration for a simple chemotherapy and therefore a cost of £173.99. The following subsequent administrations in the cycle were assumed to follow the delivery of subsequent elements of a chemotherapy cycle as recommended in the NHS Reference Costs Guidance[101] and would cost £205.09 each (Table 34). The resulting cost applied in the model per model cycle, i.e. 30.4 days, is thus equal to £252.01 for the first administration and £297.06 for each subsequent administration in the cycle.

Table 34: Unit costs of drug administration

Resource	Unit cost	Source[100]	Administration time[101]	Assumption in the model
Deliver simple parenteral chemotherapy at first attendance.	£173.99	NHS Reference costs 2016/17 - SB12Z, outpatient.	Up to 60 minutes	Applies for all cemiplimab administrations and for the first chemotherapy administration per cycle
Deliver subsequent elements of a chemotherapy cycle.	£205.09	NHS Reference costs 2016/17 - SB15Z, outpatient.	Delivery of any chemotherapy regimen other than the first attendance of a cycle.	Applies for the subsequent chemotherapy administrations within the cycle
Key: NHS, National Health Service.				

B.3.5.3. Health-state unit costs and resource use

Resource use pre-progression for ongoing care, as well as one-time costs, are summarised in Table 35; the corresponding unit costs are presented in Table 36. Similarly, the post-progression resource use is presented in Table 37 and the corresponding unit costs in Table 38. Resource use in the progression-free and post-progression health states was based on clinical experts' opinion from the Sanofi UK advisory board. In the advisory board, clinical experts were asked to indicate the resource use for patients with advanced CSCC.

In the progression-free health state, clinicians expect patients would require regular visits to their oncologist for the purposes of treatment monitoring, AE management, and the reissuing of prescriptions. As part of this treatment monitoring, it was assumed patients would undergo a blood test. Patients often have large fungating lesions on visible sites, they can become infected and foul smelling. Wound dressings can be complex and therefore regular appointments with specialist nurses are required to ensure lesions are suitably dressed and treated.

When patients move into the post-progression health state, clinicians expect a reduction in the number of oncologist visits required but an increase in the frequency of general practitioner and district nurse visits for more regular patient care, involving intensive and continual wound management.

In both the progression-free and post-progression health states it is expected a proportion of patients will receive palliative radiotherapy (RT), that is RT with a non-curative intent, for the management of bleeding and/or exudation of the wound. The dose of radiation is assumed to be given in a single fraction or fractionated if the wound is particularly large. Palliative RT was estimated to be received by 75% of patients, once every three months, in line with clinical experts' opinion. In line with a recent submission to NICE (TA489[102]), it was assumed 45% of patients would receive palliative RT and 30% would receive complex palliative RT.

Furthermore, experts interviewed in the expert elicitation exercise believed a proportion of metastatic patients will be eligible for palliative surgery, both in the pre- and post-progressive health state, to relieve soreness and pressure from the wound.

A pooled average of the data showed that 15% of patients, all of whom are metastatic and eligible for palliative surgery, would receive palliative surgery in the pre-progression health state. Following progression, 8% of patients previously treated with cemiplimab and 3% of patients previously treated with BSC would receive palliative surgery.

Table 35: Resource use in progression-free health state

Resource item	Frequency per month	Proportion of patients	Source
One-time resource use pre-progression			
Palliative surgery	1	15%	Experts interviewed as part of the expert elicitation exercise expect 15% of patients will receive surgery in the pre-progression health state.
Monthly resource use pre-progression			
Oncologist visit	2	100%	Sanofi UK advisory board: two oncologist visits per month required in the pre-progression health state.
GP visit	1	100%	Sanofi UK advisory board: one GP visit per month required in the pre-progression health state.
Blood test	2	100%	Sanofi UK advisory board: two blood tests per month required in the pre-progression health state.
Wound management nurse (community nurse)	10	100%	Sanofi UK advisory board: a minimum of 10 wound management dressings per month required in the pre-progression health state.
Wound dressings	10	100%	Sanofi UK advisory board: a minimum of 10 wound management dressings per month required in the pre-progression health state.
Tissue viability nurse	1	100%	Sanofi UK advisory board: one visit with a Specialist Tissue Viability Nurse per month required in the pre-progression health state.
Clinical specialist nurse	1	100%	Sanofi UK advisory board: one appointment with the clinical nurse specialist per month required in the pre-progression health state.
Palliative RT	0.3	45%	Sanofi UK advisory board: 75% of patients would receive a radiology appointment once every three months. NICE TA489[102], two in five RT appointments would be complex.

Resource item	Frequency per month	Proportion of patients	Source
Complex palliative RT	0.3	30%	Sanofi UK advisory board: 75% of patients would receive a radiology appointment once every three months. NICE TA489[102] two in five RT appointments would be complex.
Key: GP, General practitioner; NICE, National Institute for Health and Care Excellence; RT, RT; NICE, National Institute of Health and Care Excellence; TA, Technology Appraisal.			

Table 36: Unit costs in progression-free health state

Resource item	Unit cost	Source
UK costs		
Palliative surgery	£186.90	NHS Reference Costs 2016/17[100], JC41Z, Major Skin Procedures, Outpatient as in TA414[103]
Oncologist visit	£172.67	NHS Reference costs 2016/17[100]-WF01A-370, Non-Admitted Face-to-Face Attendance, Follow-up Medical Oncology
GP visit	£38.00	PSSRU 2017, cost of patient contact lasting 9.22 minutes[104]
Blood test	£1.13	NHS Reference costs 2016/17[100]- DAPS04, Clinical Biochemistry
Wound management nurse (community nurse)	£36	PSSRU 2017, 1 hour with a band 5 nurse community-based nurse[104]
Wound dressings	£10.18	NICE TA489, Vismodegib for treating basal cell carcinoma. Cost of wound dressings.[102]
Tissue viability nurse	£54.85	NHS Reference costs 2016/17[100] - N25AF, Specialist Tissue Viability Nursing, Face to face
Clinical specialist nurse	£82.09	NHS Reference costs 2016/17 [100]- N10AF Specialist Nursing Cancer Related, Face to face
Palliative RT (A fraction of treatment on a MV machine: 20 Gray in 5 fractions)	£107.46	NHS Reference costs 2016/17[100] - SC22Z, Deliver a Fraction of Treatment on a Megavoltage Machine

Resource item	Unit cost	Source
Complex palliative RT (A fraction of complex treatment on a MV machine: 20 Gray in 5 fractions)	£132.40	NHS Reference costs 2016/17[100]- SC23Z, Deliver a Fraction of Complex Treatment on a Megavoltage Machine
Key: GP, General practitioner; RT, RT; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.		

Table 37: Resource use in post-progression health state

Resource item	Frequency per month	Proportion of patients	Source
One-time resource use pre-progression			
Palliative surgery, following treatment with cemiplimab	1	8%	Experts interviewed as part of the expert elicitation exercise expect 8% of patients will receive surgery in the post-progression health state following treatment with cemiplimab.
Palliative surgery in the post-progression health states for chemotherapy or BSC	1	3%	Experts interviewed as part of the expert elicitation exercise expect 3% of patients will receive surgery in the post-progression health state following treatment with BSC respectively. (assumed the same for both the BSC and chemotherapy arms in the model).
Monthly resource use post-progression			
GP visit	2	100%	Sanofi UK advisory board: increased GP visits per month in the post-progression health state.
Wound management nurse (community nurse)	12	100%	Sanofi UK advisory board: increased wound management required per month in the post-progression health state.
Wound dressings	12	100%	Sanofi UK advisory board: increased wound management required per month in the post-progression health state.
Tissue viability nurse	2	100%	Sanofi UK advisory board: increased wound management required per month in the post-progression health state.
District nurse	1	100%	Sanofi UK advisory board:, one district nurse visit per month required in the post-progression health state.
Palliative RT	0.3	45%	Sanofi UK advisory board: 75% of patients would receive a radiology appointment once every three months. NICE TA489[102], two in five RT appointments would be complex.

Resource item	Frequency per month	Proportion of patients	Source
Complex palliative RT	0.3	30%	Sanofi UK advisory board: 75% of patients would receive a radiology appointment once every three months. NICE TA489[102], two in five RT appointments would be complex.
Key: GP, General practitioner; NICE, National Institute for Health and Care Excellence; RT, RT; NICE, National Institute of Health and Care Excellence; TA, Technology Appraisal.			

Table 38: Unit costs in post-progression health state

Resource item	Unit cost	Source
UK costs		
Palliative surgery	£186.90	NHS Reference Costs 2016/17[100], JC41Z, Major Skin Procedures, Outpatient as in TA414
GP visit	£38.00	PSSRU 2017[104]
Wound management nurse (community nurse)	£36	PSSRU 2017[104], 1 hour with a band 5 nurse community-based nurse
Wound dressings	£10	NICE TA489[102] Vismodegib for treating basal cell carcinoma. Cost of wound dressings.
Tissue viability nurse	£54.85	NHS Reference costs 2016/17[100] - N25AF, Specialist Tissue Viability Nursing, Face to face
District nurse	£36.93	NHS Reference costs 2016/17[100] - N02AF District nurse, Face to Face
Palliative RT (A fraction of treatment on a MV machine: 20 Gray in 5 fractions)	£107.46	NHS Reference costs 2016/17[100]- SC22Z, Deliver a Fraction of Treatment on a Megavoltage Machine
Complex palliative RT (A fraction of complex treatment on a MV machine: 20 Gray in 5 fractions)	£132.40	NHS Reference costs 2016/17[100] - SC23Z, Deliver a Fraction of Complex Treatment on a Megavoltage Machine
Key: GP, General practitioner; RT, RT; MV, Megavoltage; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.		

B.3.5.4. Adverse reaction unit costs and resource use

A description of the AEs included in the economic model and the corresponding frequencies are presented in Section B.3.3.4. All unit costs were taken from the latest NHS Reference Costs 2016/17,[100] and where codes where not similar or available from submissions, the unit costs were inflated to 2016/17 prices using the Hospital and Community Health Services (HCHS) index published by the Personal and Social Services Research Unit (PSSRU) for 2017.[104]

Table 39: Unit costs of adverse events

	Unit Cost	Reference
UK costs		
Skin infection	£143.20	Cost assumed to be the same as for cellulitis in NICE TA410[86] has been inflated using the PSSRU 2017 HCHS index.[104]
Hypercalcaemia	£1,139.92	NHS reference costs 2016/17: KC05G,H,J,K,L,M,N Fluid or Electrolyte Disorders.[100]
Failure to thrive	£3,179.70	Assumed to be same cost as fatigue.
Fatigue	£3,179.70	Cost assumed to be the same cost of fatigue as in NICE TA490,[73] has been inflated using the PSSRU 2017 HCHS index.[104]
Hypokalaemia	£1,139.92	NHS reference costs 2016/17: KC05G,H,J,K,L,M,N Fluid or Electrolyte Disorders. Weighted cost of non-elective long stay, short stay and day case.[100]
Stomatitis or oral mucositis	£998.38	Assumed to be same cost as nausea and vomiting in Brown 2013,[105] where a typical patient will have two admissions during chemotherapy, each costing £443.54. Inflated to 2016/17 prices using the PSSRU HCHS inflation indices 2017.
Neutropenia	£325.49	NHS reference costs 2016/17: WJ11Z, Other Disorders of Immunity[100]
Anaemia	£1,273.72	NHS reference costs 2016/17: SA01K, J,H,G Acquired Pure Red Cell Aplasia or Other

	Unit Cost	Reference
		Aplastic Anaemia. Weighted cost of non-elective long stay, short stay and day case.[100]
Thrombocytopenia	£325.49	NHS reference costs 2016/17: WJ11Z, Other Disorders of Immunity[100]
Febrile neutropenia	£2,688.94	The NICE DSU report[106] on the cost of febrile neutropenia 2007 (£2,286) has been inflated to 2016/17 prices using the PSSRU HCHS index 2017.[104]

B.3.5.5. Terminal care costs and resource use

A one-time cost regarding terminal care was assumed to apply for all patients. As no end-of-life data specific to patients with CSCC are available, this was applied as a single cost of £7,636.32, sourced from a study by Round *et al*. (2015),[107] which estimated the average cost of healthcare, social care and charity care for cancer patients at the end of life in England and Wales (Table 40).

Table 40: Terminal care unit costs

Resource item	Frequency per month
UK costs	
Terminal care in home	£2,189.98
Terminal care in hospital	£4,954.39
Terminal care in hospice	£491.95
Key: PSSRU, Personal and Social Services Research Unit. **Source:** Round *et al*. 2015.[107] Inflated to 0217 prices using the PSSRU 2017 HCHS inflation indices.[104]	

B.3.6. Summary of base case analysis inputs and assumptions

B.3.6.1. Summary of base case analysis inputs

A summary of all the inputs included in the cost-effectiveness model and how these were varied in the sensitivity analyses is provided in Table 41.

Table 41: Summary of variables applied in the economic model

Variable		Base case value	Low value	High value	Distribution	Reference to section in submission
Patient characteristics at baseline						
Percentage male (%)		85.0%	Not varied in sensitivity analysis			B.3.3.1
Age (years)		70.44	Not varied in sensitivity analysis			B.3.3.1
Males	Weight (kg	83.9	Not varied in sensitivity analysis			B.3.3.1
	Height (cm)	174.7	Not varied in sensitivity analysis			B.3.3.1
Females	Weight (kg)	62.1	Not varied in sensitivity analysis			B.3.3.1
	Height (cm)	158.6	Not varied in sensitivity analysis			B.3.3.1
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.				B.3.3.2
Adverse event rates for Cemiplimab						
Skin infection		0.011	0.001	0.033	Beta	B.3.3.4
Hypercalcaemia		0.021	0.004	0.051	Beta	B.3.3.4
Failure to thrive		0.077	0.008	0.213	Beta	B.3.3.4
Fatigue		0.018	0.002	0.050	Beta	B.3.3.4
Hypokalaemia		0.018	0.002	0.050	Beta	B.3.3.4
Anaemia		0.009	0.000	0.033	Beta	B.3.3.4
Adverse event rates for chemotherapy						
Hypokalaemia		0.071	0.045	0.103	Beta	B.3.3.4

Variable	Base case value	Low value	High value	Distribution	Reference to section in submission
Stomatitis or oral mucositis	0.086	0.057	0.120	Beta	B.3.3.4
Neutropenia	0.326	0.266	0.390	Beta	B.3.3.4
Anaemia	0.145	0.106	0.189	Beta	B.3.3.4
Thrombocytopenia	0.077	0.050	0.110	Beta	B.3.3.4
Febrile neutropenia	0.052	0.030	0.079	Beta	B.3.3.4
Utilities					
Progression-free survival	0.793	0.469	0.980	Beta	B.3.4.5
Post-progression survival	0.701	0.312	0.963	Beta	B.3.4.5
Adverse event utility decrements					
Skin infection	0.010	0.008	0.012	Beta	B.3.4.4
Hypercalcaemia	0.007	0.006	0.009	Beta	B.3.4.4
Failure to thrive	0.006	0.005	0.007	Beta	B.3.4.4
Fatigue	0.006	0.005	0.007	Beta	B.3.4.4
Hypokalaemia	0.007	0.006	0.009	Beta	B.3.4.4
Stomatitis or oral mucositis	0.013	0.010	0.015	Beta	B.3.4.4
Neutropenia	0.007	0.006	0.009	Beta	B.3.4.4
Anaemia	0.006	0.005	0.007	Beta	B.3.4.4
Thrombocytopenia	0.009	0.007	0.011	Beta	B.3.4.4
Febrile neutropenia	0.008	0.006	0.009	Beta	B.3.4.4
Monthly administration costs					
Cemiplimab	252.01	205.05	303.75	gamma	B.3.5.2
Cisplatin + 5FU	1,143.19	1094.32	1193.11	gamma	B.3.5.2

Variable	Base case value	Low value	High value	Distribution	Reference to section in submission
Monthly drug acquisition costs					
Cemiplimab	[redacted]	Not varied in sensitivity analysis			B.3.5.1
Cisplatin + 5FU	40.90	Not varied in sensitivity analysis			B.3.5.1
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.			B.3.5.3
Oncologist visit	2				B.3.5.3
GP visit	1				B.3.5.3
Blood test	2				B.3.5.3
Nurse wound management (community nurse)	10				B.3.5.3
Wound dressings	10				B.3.5.3
Nurse tissue viability	1				B.3.5.3
Clinical nurse specialist	1				B.3.5.3
Palliative RT	0.3				B.3.5.3
Complex palliative RT	0.3				B.3.5.3
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.			B.3.5.3
GP visit	2				B.3.5.3
Nurse wound management (community nurse)	12				B.3.5.3
Wound dressings	12				B.3.5.3

Variable	Base case value	Low value	High value	Distribution	Reference to section in submission
Nurse tissue viability nurse	2				B.3.5.3
District nurse	1				B.3.5.3
Palliative RT	0.3				B.3.5.3
Complex palliative RT	0.3				B.3.5.3
One-time costs progression-free survival					
Applied for all therapies	27.55	22.42	33.21	gamma	B.3.5.3
Monthly costs progression-free survival					
Applied for all therapies	1,011.61	823.08	1,219.28	gamma	B.3.5.3
One-time cost post-progression survival					
Applied for cemiplimab	7,650.53	6,224.78	9,221.10	gamma	B.3.5.3
Applied for chemotherapy and BSC	7,642.08	6,217.90	9,210.92	gamma	B.3.5.3
Monthly costs post-progression survival					
Applied for all therapies	805.84	655.66	971.27	gamma	B.3.5.3
Adverse event costs					
Skin infection	143.20	116.51	172.60	gamma	B.3.5.4
Hypercalcaemia	1,139.92	927.48	1,373.93	gamma	B.3.5.4
Failure to thrive	3,179.70	2,587.13	3,832.46	gamma	B.3.5.4
Fatigue	3,179.70	2,587.13	3,832.46	gamma	B.3.5.4
Hypokalaemia	1,139.92	927.48	1,373.93	gamma	B.3.5.4

Variable	Base case value	Low value	High value	Distribution	Reference to section in submission
Stomatitis or oral mucositis	998.38	812.32	1,203.33	gamma	B.3.5.4
Neutropenia	325.49	264.83	392.31	gamma	B.3.5.4
Anaemia	1,273.72	1,036.35	1,535.20	gamma	B.3.5.4
Thrombocytopenia	325.49	264.83	392.31	gamma	B.3.5.4
Febrile neutropenia	2,688.94	2,187.83	3,240.95	gamma	B.3.5.4
Other model parameters					
Model horizon	30 years	Only varied in scenario analyses			B.3.2.2
Model cycle length	1 month	Not varied in sensitivity analysis			B.3.2.2
Discount rate for costs	3.5%	Only varied in scenario analyses			B.3.2.2
Discount rate for benefits	3.5%	Only varied in scenario analyses			B.3.2.2

Key: 5-FU, 5-fluorouracil; GP, general practitioner; MV, megavoltage; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; RT, radiotherapy.

B.3.6.2. Assumptions

A summary of all the key assumptions considered in the cost-effectiveness model is provided in Table 42.

Table 42: Summary of key modelling assumptions

Assumption	Rationale	Section
Treatment comparators: cemiplimab versus chemotherapy (cisplatin) or BSC.	In the line with the scope	B.3.2.3
Time horizon: 30 years	Assumed equal to lifetime. Modelled overall survival at 30 years is less than 0.01% for all treatment arms.	B.3.2.2
Discount rate (costs and outcomes): 3.5%	NICE reference case	B.3.2.2
Perspective: NHS England perspective	NICE reference case	B.3.2.2
Cycle length: 1 month (30.4 days)	A 1-month cycle length was used in the economic model, given that the KM curves were divided into monthly cycles to generate the discrete hazards for PFS and OS.	B.3.2.2
Half cycle correction: Yes	Reduces bias	B.3.2.2
Cemiplimab dosing: Flat dose	In line with the expected license	B.3.2.3
Population: Advanced CSCC patient cohort consisting of the pooled mCSCC and laCSCC patients' data from the cemiplimab trials.	Considered appropriate to pool the two subgroups together due to: • Immaturity of the data and small patient numbers. • Limited efficacy data for comparator treatments in aCSCC. No available evidence for subgroups in the public domain. • UK clinical experts treat the two groups of patients in the same way.	B.3.2.1
Cemiplimab clinical data: overall population from the integrated analysis of the Phase I and Phase II (EMPOWER-CSCC 1) trials.	Best available evidence; Phase I data was pooled with phase II EMPOWER-CSCC 1 data as this provides the longest follow-up and increases the sample size.	B.3.3
Comparative effectiveness data of cemiplimab versus chemotherapy used in the economic model: based on	Results align with observed clinical trial and have more conservative survival results; given small number of events based on available follow-up, STC results should be interpreted with	B.3.3.2

Assumption	Rationale	Section
the naïve (unadjusted) comparison.	caution but are explored in a scenario analysis.	
PFS cemiplimab: Weibull distribution	Best fitting distribution (according to DIC) that decreases over time and results in clinically plausible long term survival estimates.	B.3.3.2
OS cemiplimab: lognormal distribution	Best fitting distribution (according to DIC) that decreases over time and results in clinically plausible long term survival estimates.	B.3.3.2
Cemiplimab treatment duration: a stopping rule is applied at 22 months – costs of treatment stop at 22 months.	Aligns with cemiplimab clinical trial design as well as previous NICE appraisals for PD-1 inhibitors.	**Error! Reference source not found.**
Cemiplimab treatment effect following the stopping rule: continuation of the treatment effect (hazard trend) up to 36 months followed by an adjustment of the hazard to be equal to the chemotherapy hazard.	Given evidence from other immunotherapies it is plausible that the cemiplimab treatment effect will continue after treatment is stopped. Given limited evidence, the duration of this effect is assumed to prolong up to 3 years. This results in more conservative long term survival when compared with experts' opinion.	**Error! Reference source not found.**
OS is capped by general mortality	To avoid implausible long-term survival estimates.	B.3.3.2
Chemotherapy (cisplatin) clinical data from the Jarkowski, 2016 study	Best available evidence with PFS and OS KM curves.	B.3.3.2
PFS chemotherapy (cisplatin): Weibull distribution	Best fitting distribution according to DIC	B.3.3.2
OS chemotherapy (cisplatin): Gompertz distribution	Best fitting distribution according to DIC	B.3.3.2
Extrapolation chemotherapy (cisplatin): continued hazard trend	Assumes treatment effects are applied for full extrapolation based on the Jarkowski et al study in a conservative assumption	**Error! Reference source not found.**
Efficacy of BSC comparator assumed to be equal to chemotherapy efficacy with zero active treatment costs applied.	Conservative assumption in the absence of BSC data in aCSCC.	B.3.3.2
Chemotherapy treatment duration: treatment costs applied up to 6 treatment cycles while the hazard trend	Aligns with the clinical practice in the UK.	**Error! Reference source not found.**

Assumption	Rationale	Section
continues as per the extrapolated curves.		
Adverse event probabilities: unadjusted estimates from clinical trials.	Best available evidence	B.3.3.4
Source of utilities: EORTC-QLQ30 values from the phase II, EMPOWER I study were mapped to EQ-5D-3L values using the Longworth *et al*. (2004) mapping algorithm.	In line with the NICE reference case. The phase II, EMPOWER CSCC 1 study provides the best available evidence in CSCC. Longworth *et al*. (2004) mapping algorithm provides best predictive ability.	B.3.4
Source of costs: published sources such as the NHS reference costs and PSSRU were used.	In line with the NICE reference case.	**Error! Reference source not found.**
Key: aCSCC, advanced cutaneous squamous cell carcinoma; BSC, best supportive care; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; laCSCC, locally advanced cutaneous squamous cell carcinoma; KM, Kaplan–Meier; mCSCC, metastatic cutaneous squamous cell cancer; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD-1, programmed death-1; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; STC, simulated treatment comparison.		

B.3.7. Base case results

B.3.7.1. Base case cost-effectiveness analysis results

Discounted results for the comparisons of cemiplimab versus chemotherapy and cemiplimab versus BSC, for both the list and the CAA proposed price, are provided in Table 43, Table 44, Table 45 and Table 46. Disaggregated results are provided in Appendix J.2.

As can be seen from the base case results below, cemiplimab demonstrates life years gained of [redacted] and a QALY gain of [redacted] and [redacted] versus chemotherapy and BSC. When cemiplimab's proposed CAA price is taken into account, there are incremental costs of [redacted] and [redacted] associated with cemiplimab over a lifetime versus chemotherapy and BSC, respectively. The incremental cost-effectiveness ratios (ICERs) versus chemotherapy and BSC are £43,740 and £46,239.

Table 43: Discounted base case results versus chemotherapy with cemiplimab list price

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

Table 44: Discounted base case results versus chemotherapy with the proposed commercial access agreement price for cemiplimab

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,740
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 45: Discounted base case results versus best supportive care with cemiplimab list price

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

Table 46: Discounted base case results versus best supportive care with the proposed commercial access price for cemiplimab

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,239
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

B.3.7.1. Clinical outcomes from the model

The results on PFS and OS from the cost-effectiveness model versus the respective results from the cemiplimab clinical trials are presented in Table 47. At the point of this submission, the outcomes on both PFS and OS from the available cemiplimab trial data are still immature, not having reached the median endpoints. Thus, comparisons of the modelled versus trial data for cemiplimab are limited. To enable an assessment of clinical validity results from the economic model where experts' opinion has been incorporated into the long-term survival extrapolations are also presented. In Table 48 the PFS and OS results from the cost-effectiveness model are compared against the observed outcomes for chemotherapy based on the Jarkowski et al study. Evidence from the Jarkowski et al study are more mature than the available evidence for cemiplimab at the point of this submission allowing thus for a longer term comparison of the modelled outcomes with the observed data.

The model is generally shown to produce accurate survival estimates which are in line with the observed data from the cemiplimab clinical trials and the Jarkowski et al study. No specific patterns of over or under estimation of the observed data was found with sporadic diversities not deemed to be clinically significant. This becomes particularly apparent when the base case modelled outcomes are compared against the outcomes based on experts' opinion. As can be seen from the results below when these outcomes are compared, the base case modelled long term survival estimates are more conservative than those incorporating expert opinion. It is notable that the cemiplimab predictions are in line with the 5-year survival rates reported for pembrolizumab and nivolumab in advanced melanoma of 34%.[108, 109] In addition, UK clinical experts consulted at a Sanofi advisory board indicated that survival for advanced CSCC patients treated with chemotherapy in the UK would not exceed 5% at 2 years. The survival estimate from the economic model for chemotherapy at 2 years is 34.5% reinforcing thus that in the base case analysis the assumptions adopted in the model could have led to an overestimation of the chemotherapy survival benefit when considering current experience in the UK clinical practice.

Table 47: Cemiplimab modelled results versus the observed clinical data

Outcome		Clinical data	Results from the economic model (base case)	Results from the economic model with experts' opinion[a]
PFS	3 months	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]
	24 months	N/A	[redacted]	[redacted]
	5 years	N/A	[redacted]	[redacted]
	10 years	N/A	[redacted]	[redacted]
OS	3 months	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]
	24 months	N/A	[redacted]	[redacted]
	5 years	N/A	[redacted]	[redacted]
	10 years	N/A	[redacted]	[redacted]

Key: N/A not available; OS, overall survival; PFS, progression-free survival.
Note: [a], Results that include the experts' opinion on long term survival estimates from the formal elicitation exercise using the best fitting distributions.

Table 48: Chemotherapy modelled results versus the observed clinical data

Outcome		Clinical data[a]	Results from the economic model (base case)	Results from the economic model with experts' opinion[b]
PFS	3 months	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]
	24 months	[redacted]	[redacted]	[redacted]
	5 years	N/A	[redacted]	[redacted]
	10 years	N/A	[redacted]	[redacted]
OS	3 months	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]
	24 months	[redacted]	[redacted]	[redacted]
	5 years	N/A	[redacted]	[redacted]
	10 years	N/A	[redacted]	[redacted]

Key: N/A not available; OS, overall survival; PFS, progression-free survival.
Notes: [a], The clinical data represents the digitized KM plots from the Jarkowski 2016 publication [b], Results that include the experts' opinion on long term survival estimates from the formal elicitation exercise using the best fitting distributions.

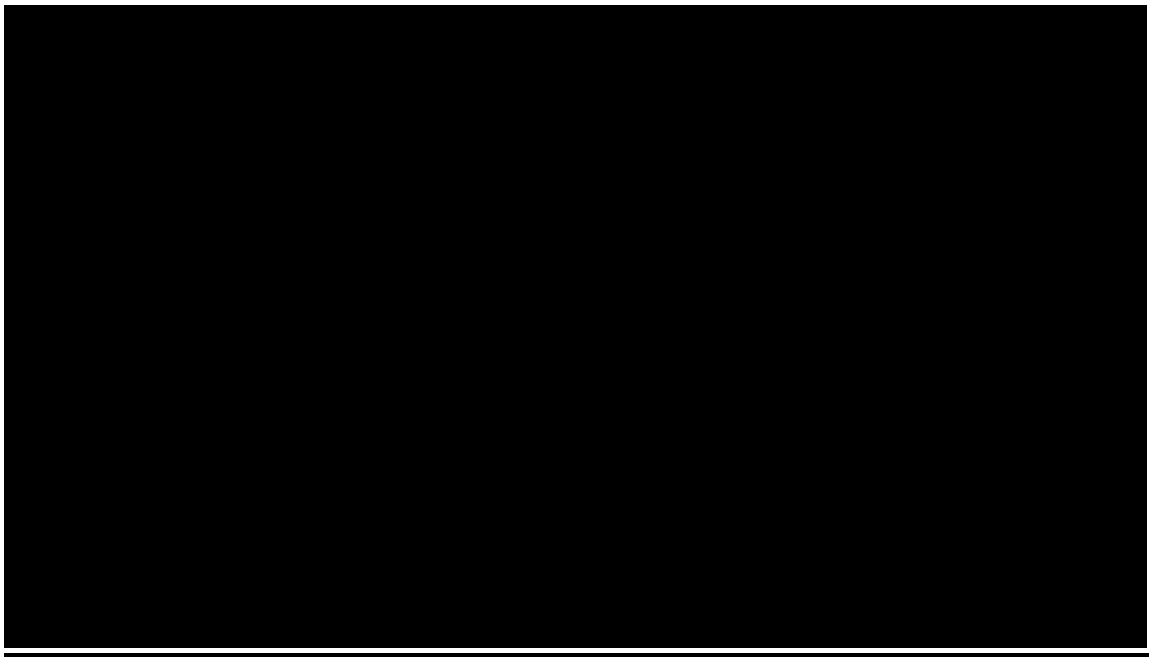
B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were conducted for the different base case scenarios presented above. A second-order Monte Carlo simulation was run for 1,000 iterations for each analysis in order to account for the uncertainty in the model parameters. Results from the comparison of cemiplimab against chemotherapy and BSC for the list and the proposed CAA price are presented in Figure 35 to Figure 42 on cost-effectiveness planes and as cost-effectiveness acceptability curves. Summary results are also available in Appendix Q.

When the proposed CAA price is taken into account, cemiplimab has a probability of being cost-effective of 55% versus chemotherapy and 50% versus best supportive care whereas the reported ICERs show consistent results when compared with the respective deterministic ones. This level of uncertainty is to be expected given the underlying evidence base. Collection of data whilst on the CDF would increase the certainty surrounding these cost-effectiveness estimates whilst allowing immediate access to cemiplimab for patients with a very high unmet medical need.

Figure 35: Cost-effectiveness plane of cemiplimab versus chemotherapy with cemiplimab list price

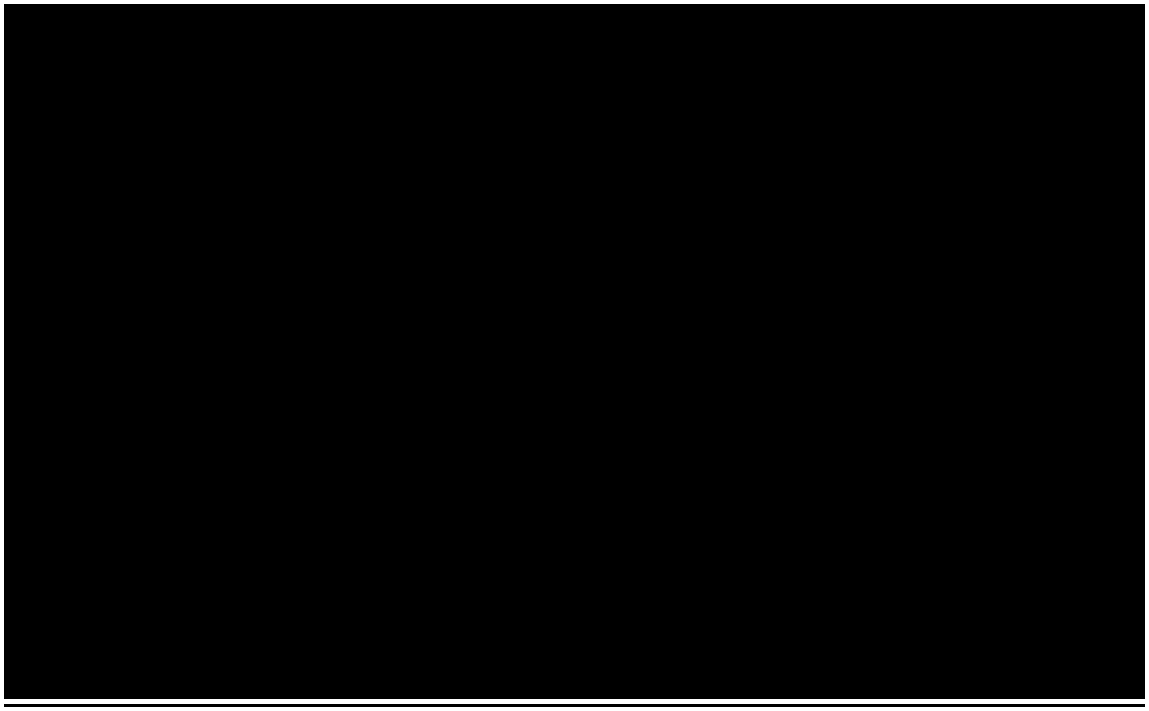


Key: QALYs, quality adjusted life years; WTP, willingness to pay.

Figure 36: Cost-effectiveness Acceptability Curve (CEAC) of cemiplimab versus chemotherapy with cemiplimab list price

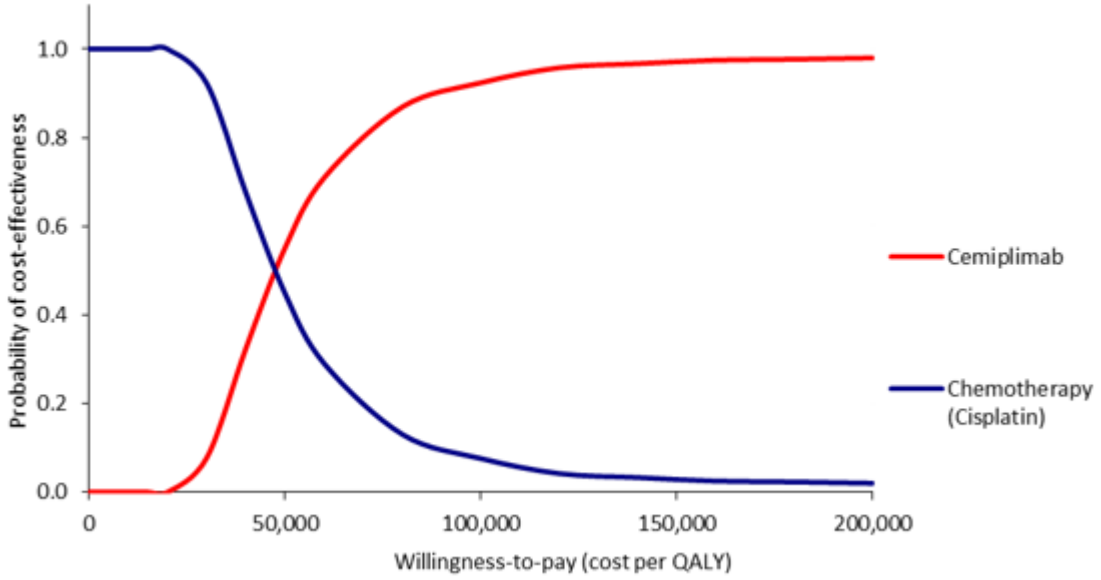
Key: QALYs, quality adjusted life years.

Figure 37: Cost-effectiveness plane of cemiplimab versus chemotherapy with the proposed commercial access agreement price for cemiplimab



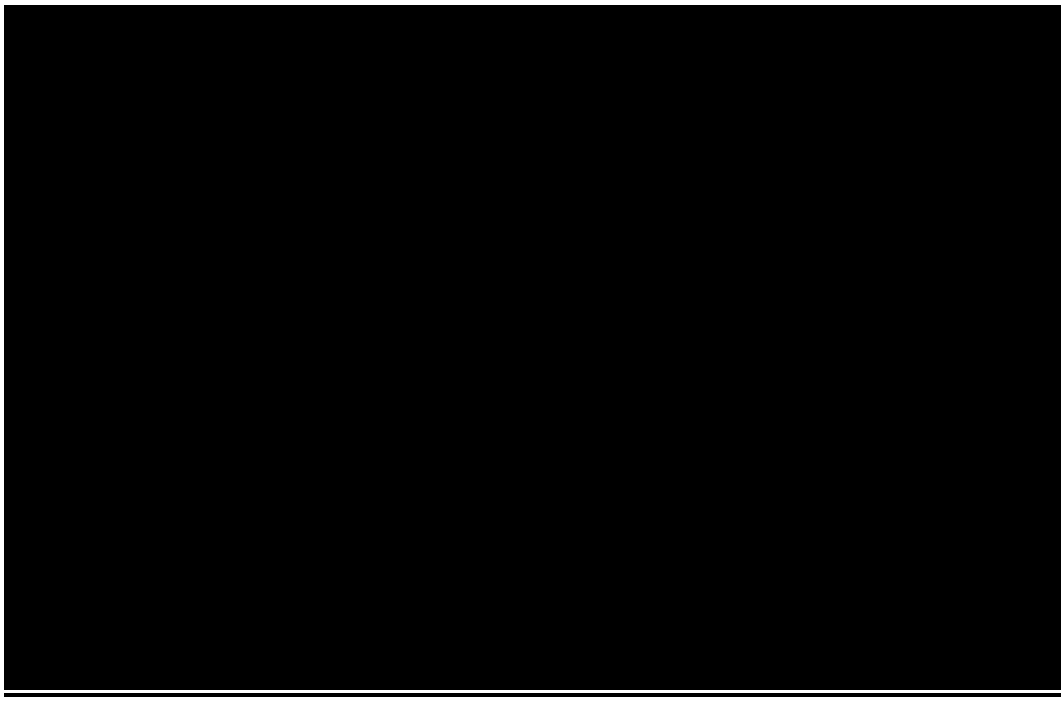
Key: QALYs, quality adjusted life years; WTP, willingness to pay.

Figure 38: Cost-effectiveness acceptability curve (CEAC) of cemiplimab versus chemotherapy with the proposed commercial access agreement price for cemiplimab



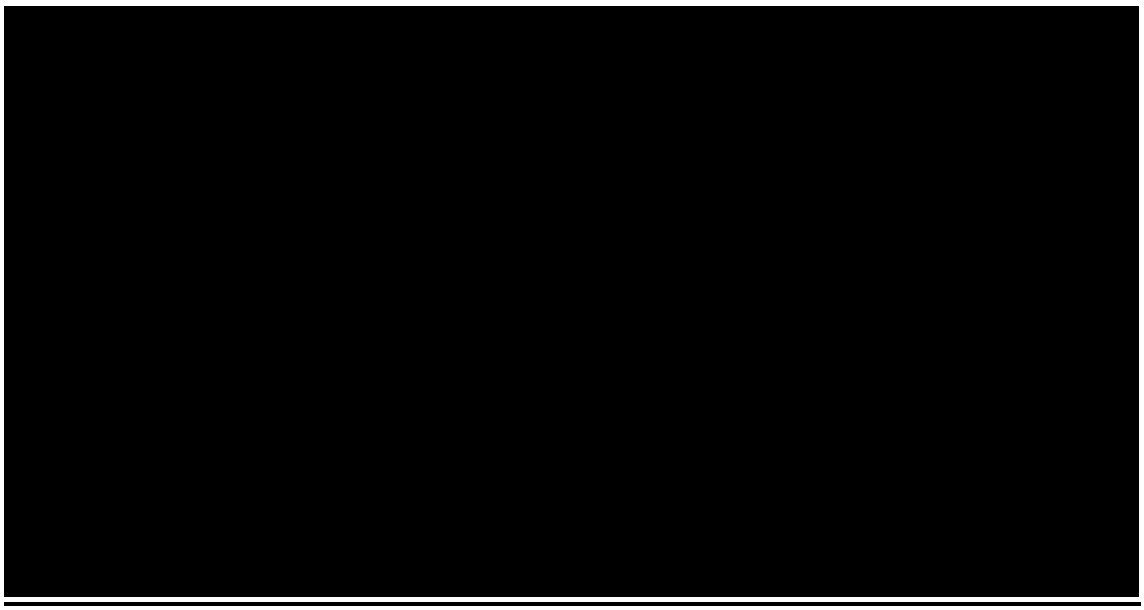
Key: QALYs, quality adjusted life years.

Figure 39: Cost-effectiveness plane of cemiplimab versus best supportive care with cemiplimab list price



Key: QALYs, quality adjusted life years; WTP, willingness to pay.

Figure 40: Cost-effectiveness Acceptability Curve (CEAC) of cemiplimab versus best supportive care with cemiplimab list price

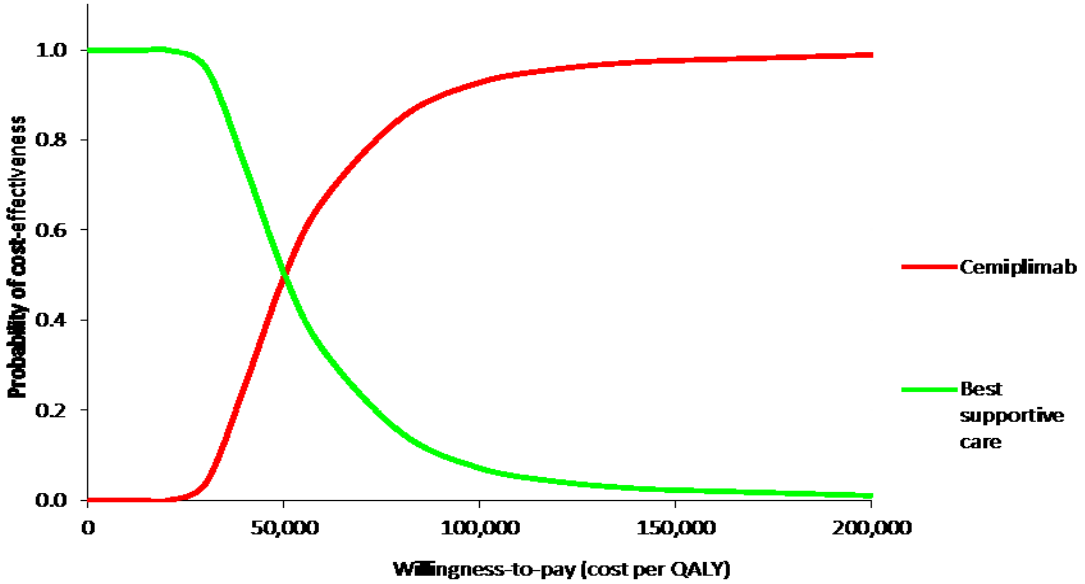


Key: QALYs, quality adjusted life years.

Figure 41: Cost-effectiveness plane of cemiplimab versus best supportive care with the proposed commercial access agreement price for cemiplimab

Key: QALYs, quality adjusted life years; WTP, willingness to pay.

Figure 42: Cost-effectiveness Acceptability Curve (CEAC) of cemiplimab versus best supportive care with the proposed commercial access agreement price for cemiplimab



Key: QALYs, quality adjusted life years.

B.3.8.2. Deterministic sensitivity analysis

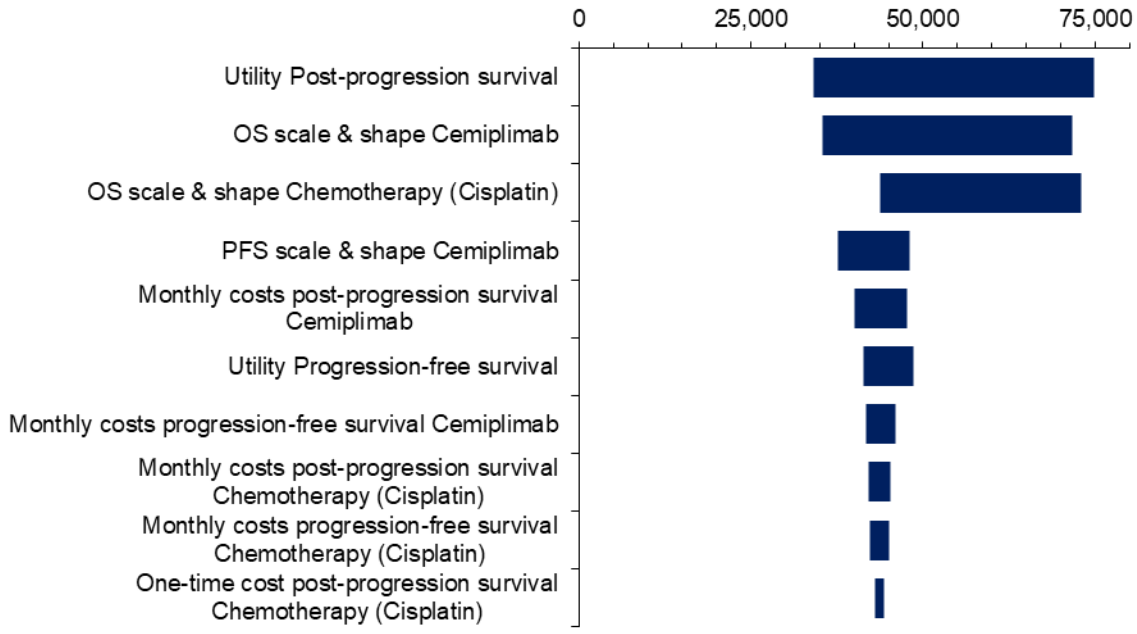
Deterministic sensitivity analyses (SAs) were conducted to explore uncertainty around model inputs. Tornado diagrams in Figure 43 up to Figure 46 show how the ICERs using both the list and CAA price vary when the 10 most influential inputs are varied. The key drivers of cost-effectiveness were found to be the utility values used in the progression-free health state alongside the shape and scale parameters for OS and PFS.

Figure 43: Tornado diagram for one-way sensitivity analyses of cemiplimab versus chemotherapy with cemiplimab list price

[redacted]

Key: OS, overall survival; PFS, progression-free survival.

Figure 44: Tornado diagram for one-way sensitivity analyses of cemiplimab versus chemotherapy with cemiplimab proposed CAA price



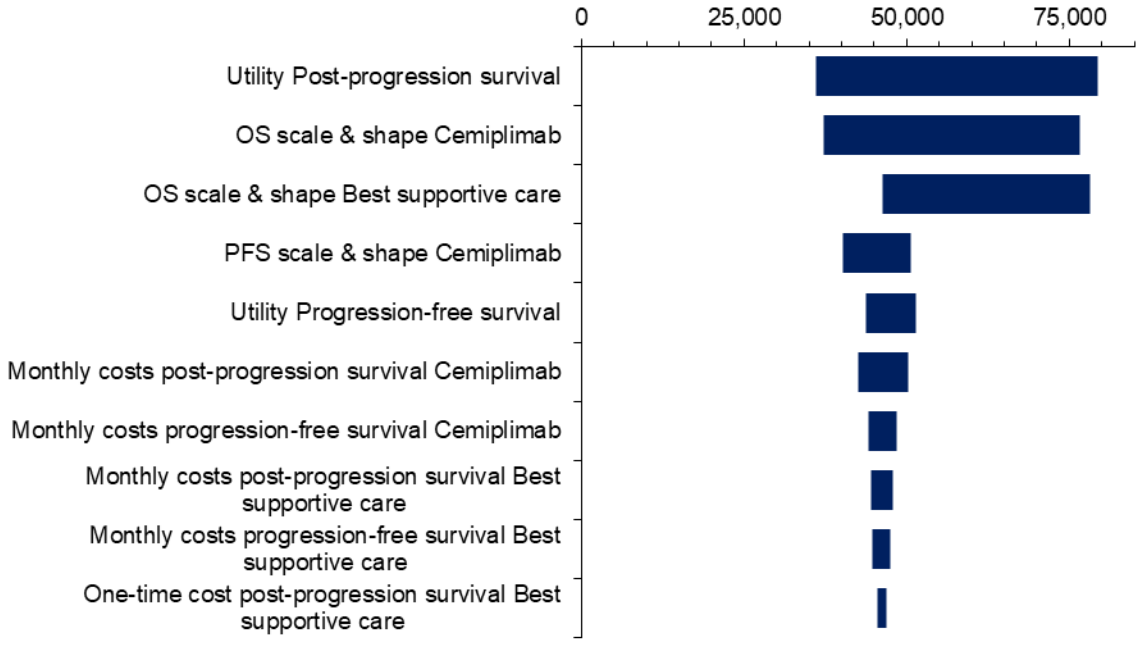
Key: OS, overall survival; PFS, progression-free survival.

Figure 45: Tornado diagram for one-way sensitivity analyses of cemiplimab versus BSC with cemiplimab list price

[redacted]

Key: OS, overall survival; PFS, progression-free survival.

Figure 46: Tornado diagram for one-way sensitivity analyses of cemiplimab versus BSC with cemiplimab proposed CAA price



Key: OS, overall survival; PFS, progression-free survival.

B.3.8.3. Scenario analyses

To further explore uncertainty around key assumptions in the model, a series of scenario analyses were conducted. These are presented in Table 49 alongside the resulting ICERs versus chemotherapy and BSC.

Table 49: Results of scenario analyses with cemiplimab commercial access agreement price

Base case input	Scenario	ICER versus chemotherapy	ICER versus BSC
Base case results	**N/A**	**43,740**	**46,239**
Comparative efficacy: Naïve	STC[a]	38,238	39,952
22 month stopping rule	24 month stopping rule	45,628	48,132
Assumption regarding continued treatment benefit following the 22-month treatment cap: 3-year cap	Continued benefit	36,217	38,039
	22-month cap	56,647	60,316
	5-year cap	37,726	39,688
	Constant hazard after 22 months	49,532	52,538
	Waning effect between 22 months to 5 years	40,938	43,189
Source of cemiplimab data: Integrated analysis of phase I and phase II trials	Phase II + naïve comparison	57,632	61,559
Alternative curve fits for cemiplimab: OS	Gompertz	37,259	39,194
	Weibull	43,891	46,402
Alternative curve fits for cemiplimab: PFS	Lognormal	43,460	45,956
	Log-logistic	43,376	45,876
Alternative curve fits for chemo: OS	Lognormal	56,607	60,259
	Second-order fractional polynomial P1=1, P2=0	41,064	43,326
Alternative curve fits for chemo: PFS	Lognormal	43,306	45,748
	Gompertz	43,742	46,215
Cemiplimab time on treatment assumed equivalent to time to progression	Adjustment factor applied for time on treatment	38,490	40,972

Base case input	Scenario	ICER versus chemotherapy	ICER versus BSC
Alternative chemotherapy treatment cycles: maximum of 6 treatment cycles	Maximum of 3 treatment cycles	44,699	N/A
Utilities: EQ-5D mapped from Phase II EORTC-QLQ30	Different algorithm (McKenzie)	42,612	45,042
	SCCHN utilities (mSCCHN) (TA473)	56,947	60,253
	ERIVANCE trial laBCC population	40,710	43,027
	ERIVANCE trial mBCC population	46,436	49,097
Population: Pooled	Locally advanced	43,057	45,042
	Metastatic	45,642	48,622
Time Horizon: 30 years	20 years	44,614	47,205
	10 years	53,812	57,281
	5 years	75,037	80,563
Discount rate: 3.5% for costs + QALYs	0%	37,973	39,880
	6%	47,940	50,885
	1.5%	40,417	42,572
Efficacy of BSC: equal to chemotherapy	Pooled EGFR studies	N/A	39,047
	All studies pooled	N/A	40,098
Long term extrapolations of cemiplimab, chemotherapy and BSC: based on the integrated analysis of cemiplimab trials and Jarkowski et al 2016	Based on the cemiplimab phase II trial + experts' elicitation and Jarkowski et al 2016 + experts' elicitation[a]	30,112	31,389

Key: BSC, best supportive care; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core-30; mSCCHN, metastatic squamous cell carcinoma of the head and neck; N/A, not applicable; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; SCCHN, squamous cell carcinoma of the head and neck; STC, simulated treatment comparison.
[a]using best fitting curves based on DIC

B.3.8.4. Summary of sensitivity analyses results

When parameter uncertainty was examined in the probabilistic sensitivity analyses, results generated were in line with the respective deterministic values, thus demonstrating consistency between the different analyses. However, the likelihood

of cemiplimab being cost effective versus chemotherapy and BSC at a willingness-to-pay threshold of £50,000/QALY was 55% and 50% respectively which demonstrates the level of uncertainty associated with the currently available evidence. This level of uncertainty is to be expected given the underlying evidence base. Collection of data whilst on the CDF would increase the certainty surrounding these cost-effectiveness estimates whilst allowing immediate access to cemiplimab for patients with a very high unmet medical need.

When individual model inputs were varied around their mean value in the one-way sensitivity analysis (OWSA), the key drivers of cost-effectiveness were found to be the utility values used in the progression-free health state alongside the shape and scale parameters for OS and PFS.

An extensive range of scenario analyses were conducted to examine the effect of alternative assumptions and structural changes in the model results. The majority of these analyses report ICERs below £50,000/QALY (where the proposed CAA price is used). Notably where expert opinion was incorporated ICERs were significantly below £50,000/QALY (£30,112 versus. chemo and £31,389 versus BSC). Together these should reassure the committee that cemiplimab has the potential to be a cost-effective use of NHS resources.

B.3.9. Interpretation and conclusions of economic evidence

A comprehensive approach has been taken to demonstrate the cost-effectiveness of cemiplimab versus the current standard of care. Although the analysis is based on data from the largest prospective cohort of CSCC patients, survival data for this cohort is currently immature and results rely on extrapolating this data over the longer term. Furthermore, there is no randomised comparator data available and data from the literature or existing databases is scarce. This means the analysis is based on naïve unadjusted comparison or population adjusted comparison versus small observational studies. Together, this results in a considerable amount of uncertainty which is reflected in the probabilistic sensitivity analysis (PSA) and underpins our proposal that cemiplimab be considered for use on the CDF. Acknowledging this uncertainty, attempts have been made to incorporate clinical opinion (both informally and formally) where possible.

Despite limitations regarding the available evidence, using a credible and clinically plausible set of assumptions, cemiplimab is shown to be cost effective versus BSC and chemotherapy as an end-of-life treatment. Moreover, extensive scenario analyses demonstrate cemiplimab remains cost effective in the majority of scenarios explored. Collection of data whilst on the CDF would increase the certainty surrounding these cost-effectiveness estimates whilst allowing access to cemiplimab for patients with a particularly poor prognosis for whom there are no licenced or effective alternatives.

B.3.10. Validation

B.3.10.1. Validation of cost-effectiveness analysis

The cost-effectiveness model was thoroughly validated during the different stages of development, from the early conception through to finalisation, in line with the recommendations by the International Society for Pharmacoeconomics and Outcomes Research Society and the Society for Medical Decision-Making Joint Task Force for Modelling Good Research Practices.[110]

These guidelines stress the importance of face validity (confirming the model approach, data sources, and assumptions with experts), internal validity (quality-checking of parameter values and calculations), and external validity (comparing model results with other published studies).

As previously described in the early conceptualisation phase of the cost-effectiveness model, the proposed model structure alongside the key parameters and assumptions were presented and discussed with UK key opinion leaders during an advisory board conducted by Sanofi. On top of this, the key assumptions and structural updates were continuously validated through the development process with both UK and international experts' input. In particular, experts' opinion was formally elicited and incorporated in the model in an effort to bridge the gap of evidence observed in the public domain around advanced CSCC and the long-term efficacy of the current therapies.

During the development process the model underwent the following stages of internal validation:

- Technical verification and evaluation of internal consistency to ensure there were no structural, calculation or programming errors. This technical verification was performed by a modeller not involved in the programming of the model who checked formulas, calculations, links between cells (in Microsoft Excel®) and syntax (in Visual Basic®).
- Sensitivity analysis of all parameters and extreme value analysis was performed to determine whether the model output was as expected and to help identify any remaining errors.
- As a last step, internal consistency was evaluated by comparing the model outputs with source data used for the model development.

After model finalisation, cross-validation was performed by comparing the results of the developed model for the interventions of interest with results obtained with models reported in the literature, wherever available, to ensure plausibility of results. External validation against previously conducted economic evaluations in CSCC was not possible as this is the first cost-effectiveness model for the treatment of advanced CSCC. However, external validation was performed by indirectly comparing the cost-effectiveness model findings with previously performed cost-effectiveness analyses in other types of tumour. Furthermore, the extrapolated OS estimates were compared with general, UK-specific life table results to ensure the cost-effectiveness model provided meaningful results. Based on the findings of the above process, the model was corrected and updated where necessary.

Finally, the cost-effectiveness model was also validated by a third independent external modelling team. The overall model structure, methods, assumptions and values applied to model input parameters were reviewed to confirm that the correct clinical pathway for patients with CSSC has been modelled. To ensure the model structure was appropriate, the model was compared against the NICE reference case, and a number of previous NICE submissions within the clinical areas of cell carcinoma and melanoma skin cancer were reviewed, alongside each corresponding evidence review group (ERG) report. The data sources for all model input parameters were also reviewed to ensure they are appropriate for a NICE submission. A specific validation checklist was employed that allowed for the

application of a range of tests, including assessing the credibility and face validity of the model.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Baseline characteristics and additional efficacy outcomes

Appendix M: Expert elicitation of long-term survival for patients with advanced CSCC treated with platinum chemotherapy or cemiplimab

Appendix N: Mapping HRQL

Appendix O: Proposed data collection for inclusion on the Cancer Drugs Fund

Appendix P: Alternative scenarios for BSC efficacy where EGFR studies are pooled with or without Jarkowski study

Appendix Q: Probabilistic sensitivity analyses

Appendix R: Scenario analyses with cemiplimab list price

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Single technology appraisal

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

Dear [redacted],

The Evidence Review Group, SHTAC, and the technical team at NICE have looked at the submission received on 25 October 2018 from Sanofi. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Friday 30 November 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Rufaro Kausi, Health Technology Assessment Advisor ([redacted]). Any procedural questions should be addressed to Thomas Feist, Project Manager ([redacted]).

Yours sincerely

[redacted]
Health Technology Assessment Adviser- Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Clinical effectiveness studies

A1. Please provide the PDF including any supplemental material, for Gold 2018 which is cited but not listed.

A2. **Priority question**. The description of the 56 studies included in the SLR feasibility assessment reported in section D.1.3.1 and also in section D.1.3.2 is not fully clear, as the statements made about the 54 potential comparator studies do not identify specific studies. Also, the numbers of studies discussed at each step of feasibility assessment do not sum to 56 (the "remaining pool" of studies is referred to as being both n=18 and n=17). Given that the selection of appropriate comparator studies is a critical part of the technology appraisal, please justify your study selection by providing a clear tabulation of the 54 potential comparator studies, indicating the following for each study:

- The study design
- The population (laCSCC, mCSCC, combined)
- Age
- ECOG PS
- Any systemic therapies used
- Any surgeries used
- Any radiotherapies used
- Primary tumour site
- Immunosuppression
- Whether K-M curves were reported for OS
- Whether K-M curves were reported for PFS
- Any prognostic variables reported as listed in Table 8 of section D.1.3.3

A3. **Priority question**. The consideration of relevant comparators in section B.2.9.1 and in Appendix D does not explicitly discuss whether any of the identified studies could have provided any relevant data on BSC. Please clarify whether any studies have control arms or subgroups that could be relevant? (e.g. non-platinum-treated patients

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in the Jarkowski study or other studies?). Were any of the excluded studies of surgery in populations that might serve as surrogates for BSC?

A4. **Priority question**. Median follow-up was 11.1 months (range 1.1 to 17) in the phase I study (section B.2.3.1), 8.6 months (range 0.8 to 15.9) in EMPOWER-CSCC (section B.2.3.2), and 8.56 months (0.8-15.9 months) for the integrated analysis (section B.2.4).

(a) Please explain why the follow-up in the integrated analysis is shorter than for either of the constituent studies.

(b) Please explain how the minimum follow-up can be 0.8 months in the EMPOWER-CSCC study and 1.1 months in the phase I study if there are no patients in either study with follow up <9 months?

(c) Please provide the median (range) follow-up for the laCSCC and mCSCC subgroups in each study. For the laCSCC subgroup in the EMPOWER-CSCC study please provide the length of follow-up (i) including the 32 patients who had follow-up less than 9 months and (ii) excluding the 32 patients who had follow-up less than 9 months.

(d) Please provide the median (range) follow-up for the non-CSCC patients in the phase I study (to assist the ERG to interpret the safety data).

A5. Table 5 in section B.2.3.2.2 reports the baseline characteristics for the full EMPOWER-CSCC study (i.e. groups 1+2+3; n=137). Please provide the baseline characteristics for the subgroup from the EMPOWER-CSCC study included in the FAS (i.e. n=82).

A6. Please provide the reference and PDF, including any supplemental material, for the review by Yanagi et al 2018 which is referred to in section D.1.2.1.

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Identification of prognostic factors for CSCC

A7. Please provide the references and PDFs for the 28 studies of prognostic factors for CSCC that are summarised in Appendix D.1.3.3.

A8. Please explain how the results of the search were "validated by consulting clinicians…" as stated in section B.2.9.1.1, and the number of clinicians that were consulted.

A9. Please explain the format of Table 8 in Appendix D, as this is not fully intuitive. Do the numbers reported in columns 3-6 refer to the number of studies? What is the difference between "Reported" and "Significant"? What does "Data availability in studies included in the analysis" mean? Please indicate which studies provided the data that are shown in each cell of the table, as these data cannot be traced to specific studies.

Clinical effectiveness data analysis

A10. Figure 7 in section B.2.3.1.3 indicates that data should be available for 23 patients who received cemiplimab 350 mg q3w. Please provide clinical effectiveness outcomes for OS, PFS, ORR and DOR for these patients. If possible, please also provide the baseline characteristics for these patients.

A11. **Priority question**. The matching employed in the MAIC and STC analyses assumes by default that the Jarkowski study is the "real world" target population relevant to this technology appraisal. This is a critical assumption but the study is very small (25 participants), retrospective (so at risk of bias) and few details of the population are reported. Please explain why a better estimate of the target population has not been provided. Could the retrospective chart review referred to in section B.2.11 provide a more relevant target population? Please provide the details of the chart review population.

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A12. Section B.2.9: Please provide the weights given to each patient in the MAIC. We are interested in whether certain patients are driving the analysis and how they correspond to the real-world population.

A13. Section B.2.3.1.3 states that 32 participants from the EMPOWER-CSCC study were excluded from the FAS as they did not complete at least 9 months follow-up (to allow minimum duration of response of 6 months as per FDA recommendation). Please provide an analysis, with the HR or OR and confidence interval where appropriate, that includes these 32 patients for the outcomes specified in the decision problem (OS, PFS, ORR, DOR):

(a) For the integrated analysis FAS (i.e. n=140).

(b) For the integrated analysis laCSCC subgroup (i.e. n=65) and for the EMPOWER-CSCC study laCSCC subgroup (n=55).

A14. For Table 10 in Appendix D.1.3.5 please provide definitions for the core model and the different extended models, and which covariates were included in each, as these models are not fully explained in section B.2.9.2.3.

A15. Section B.2.9.2.3 states that the coefficients for the extended models differed in a direction contrary to what was expected. Please provide the covariates and their coefficients.

A16. Appendix D.1.3.6 briefly mentions the programming language for the STC and MAIC analyses. Please provide the full R statistical code used for these analyses, together with the IPD data used in the model for the cemiplimab and Jarkowski studies.

A17. Did the company assess the proportional hazards assumption for OS and PFS in the MAIC analysis? The submission states above Fig 23 (section B.3.3.2.1) that the proportional hazard (PH) assumption was not expected to be valid. However, results of a PH test are reported in Fig 23 and the company submission reports constant hazards as the output from the matching analysis. Please explain how PH were

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assessed for each relevant comparison (what test does the p-value reported in Figure 23 refer to?). If the PH assumption was not satisfied please explain the implications of this for interpreting the results?

A18. The EGFR inhibitors cetuximab, gefitinib and erlotinib are included as overlaid observed data in the MAIC/STC analysis results in section D.1.3.5. Given that these therapies are outside of the NICE scope and the company's decision problem, the rationale for these comparisons is unclear. Please provide an explanation for these naïve unanchored comparisons of cemiplimab against the EGFR inhibitors.

A19. Section D.1.3.1: Is the statement that dacomitinib and panitumumab are unlikely to be used to treat advanced CSCC patients based on assumption or evidence? Please provide evidence if possible.

Validation of the dosing regimen

A20. Section B.2.3.1.2 states that "Safety and efficacy data from this 3mg/kg q2w regimen are used to support the proposed dose regimen (350 mg q3w) based on pharmacokinetic (PK) modelling and simulation of exposure, and supported by observed data at 350 mg q3w".

(a) Please provide the results of the PK modelling, and sufficient information on the methods as necessary to enable these results to be interpreted unambiguously.

(b) Please provide the observed exposure data for 350 mg q3w.

Safety

A21. Table 25 in section B.3.3.4: How were these adverse events selected? Please clarify why the percentages in Table 25 differ slightly from those in Table 13 (section B.2.10.2).

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Other issues related to cemiplimab mode of action

A22. Please confirm whether PD-L1 expression was measured in the patients with CSCC? Does the company plan to measure PD-L1 expression and perform any analyses by PD-L1 expression subgroups?

A23. Please confirm whether the development of anti-therapeutic (or "anti-drug") antibodies to cemiplimab was monitored? If so please report the rates and comment on how these compare against other PD-L1 inhibitors.

Section B: Clarification on cost-effectiveness data

B1. **Priority question.** The ERG has been unable to replicate cost-effectiveness results presented by the company for the scenarios listed below. Please comment on the following discrepancies in the CE results:

Scenario	Company's results		ERG results	
	ICER vs CT	ICER vs BSC	ICER vs CT	ICER vs BSC
Comparative efficacy: STC	£38,238	£39,952	£36,875	£38,490
Treatment benefit cap at 5 years	£37,726	£39,688	£39,247	£41,346

B2. **Priority question.** The ERG was unable to run the following cost-effectiveness scenarios. Please explain how you conducted these analyses in the submitted model:

(a) Using a maximum of 3 treatment cycles for chemotherapy treatment.

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(b) “Long-term extrapolation of cemiplimab, chemotherapy and BSC based on the cemiplimab phase II trial + experts’ elicitation and Jarkowski et al 2016 + experts elicitation” (as written in Table 49 in section B.3.8.3)

B3. **Priority question.** The adverse event rates for cemiplimab in the model (CS Table 25 in section B.3.3.4) are not consistent with the modelled treatment, as patients receiving a flat dose were excluded. The included types of adverse event and event rates are also inconsistent with results reported for the safety analysis set in CS section B.2.10.2 Table 12 and 13.

Please explain how you derived the lists of included events and the event rates in Tables 25 and 26.

Please also provide a complete list of adverse events from the integrated analysis safety population (n=163) comparable to Table 3 for the Platinum-Fluorouracil arm of the Vermorken et al study (NEJM 2008). This should include all grade 3-5 events with an incidence of 1% or higher in either study.

B4. Please explain the rationale for your selection of adverse event utility decrements in Table 27 (section B.3.4.4) and costs in Table 39 (section B.3.5.4). Why did you select different NICE technology appraisals as the sources for different adverse events?

Please also explain why you apply the same assumed duration of 30 days for all adverse events?

B5. PFS and OS estimates from expert elicitation are presented for chemotherapy in Figures 31 and 32 (section B.3.3.2.5). However, for cemiplimab, estimates from expert elicitation are only presented for OS (Figure 26) but not for PFS (section B.3.3.2.3). Please explain whether there is a reason for this difference between the modelled treatments?

Section C: Textual clarifications and additional points

C1. Please provide footnotes a and b for Figure 4 in section B.2.1.

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C2. Please provide footnote a for Table 7 in Appendix D.

C3. Please provide footnote c for Table 8 in Appendix D.

C4. In Table 18 in section B.3.3.1 the sample sizes reported in the “Source/justification” column are the same for males and females. Please confirm whether these are typos?

C5. The title to Figure 31 in section B.3.3.2.5 states that observed PFS data was combined with OS from the expert elicitations. Please confirm whether this is a typo?

[redacted]

National Institute for Health and Care Excellence
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30th November 2018

Dear [redacted],

Re: Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

Thank you for the opportunity to provide our answers to the clarification questions posed by the Evidence Review Group and technical team at NICE for this appraisal. Please find our responses attached. As requested we provide two versions of our written response; one with commercial-in-confidence information clearly marked and one with this information redacted. We also provide a checklist of confidential information.

If you have any queries or require further clarifications please don't hesitate to contact us.

Yours Sincerely,

[redacted]
Senior Health Outcomes Manager
UK & Ireland
Tel: [redacted]
[redacted]

Section A: Clarification on effectiveness data

Clinical effectiveness studies

A1. Please provide the PDF including any supplemental material, for Gold 2018 which is cited but not listed.

The PDF for this study has been attached to this response (there was no supplementary material).

A2. Priority question. The description of the 56 studies included in the SLR feasibility assessment reported in section D.1.3.1 and also in section D.1.3.2 is not fully clear, as the statements made about the 54 potential comparator studies do not identify specific studies. Also, the numbers of studies discussed at each step of feasibility assessment do not sum to 56 (the "remaining pool" of studies is referred to as being both n=18 and n=17). Given that the selection of appropriate comparator studies is a critical part of the technology appraisal, please justify your study selection by providing a clear tabulation of the 54 potential comparator studies, indicating the following for each study:

- **The study design**
- **The population (laCSCC, mCSCC, combined)**
- **Age**
- **ECOG PS**
- **Any systemic therapies used**
- **Any surgeries used**
- **Any radiotherapies used**
- **Primary tumour site**
- **Immunosuppression**
- **Whether K-M curves were reported for OS**
- **Whether K-M curves were reported for PFS**
- **Any prognostic variables reported as listed in Table 8 of section D.1.3.3**

Fifty-six studies (represented by 57 citations) were initially included in the SLR. However, one additional study (Gold 2018) was identified via hand search at a later

time and added to the evidence base. Therefore, a total of 57 studies (represented by 58 citations) were reviewed for the purpose of the feasibility assessment.

Of the 57 studies that were reviewed, 39 only included patients with regional metastasis and featured surgical interventions with curative intention. As stated in section B.1.3, the population of interest for this submission includes patients with metastatic disease (mCSCC) and patients with locally advanced disease (laCSCC) who are not candidates for surgery or curative radiotherapy. Therefore, these studies were considered not comparable to the cemiplimab trials in terms of the recruited population (as discussed in section D.1.3.1) and were excluded from the analysis. A summary of the above mentioned 39 studies is presented in **Table 1**.

The remaining pool of 18 studies included 16 comparator studies (summarised in **Table 2**) as well as the two cemiplimab trials. As discussed in section D.1.3.1, all these studies featured systemic therapies, which are assumed to generally be used to treat advanced CSCC regardless of subgroup. One study recruited only patients with laCSCC and one only recruited patients with mCSCC (regional and/or distant); both also featured systemic therapies.

All but three of the prognostic factors identified through our targeted search are already included in **Table 1** and **Table 2**. The three tumour characteristics not included in the summary tables (differentiation grade, perineural invasion, and size/depth) were generally not reported across the included studies and are, therefore, briefly summarised in **Table 3** only for those studies (out of the 57) that reported at least one of them.

Table 1: Summary of the 39 studies that were entirely conducted among regionally metastatic patients and featured surgical interventions

Study	Population	N	Age, median (range)	Male	ECOG PS	Intervention groups				Primary tumour site			Immuno-compromised	Prior treatment experience			KM curves	
						Sx alone	Sx + adj. RT	Sx + adj. CRT	RT alone	H&N	Trunk	Extremities		Sx	RT	CT	OS	PFS
Prospective observational studies																		
Kelder 2012	Regional mCSCC	164	73 (25-98)	142 (87)	--	33 (20)	131 (80)	--	--	164 (100)	0 (0)	0 (0)	--	--	--	--	Yes	No
Moore 2005	Regional mCSCC and resectable local CSCC	40[a]	68 (34-89)	35 (88)	--	--	--	--	--	40 (100)	0 (0)	0 (0)	--	--	--	--	Yes	No
O'Brien 2001	Melanoma of the parotid (n=50) or CSCC with metastasis to the parotid gland (n=73)	73	70	63 (86)	--	58 (80)	15 (21)	--	--	--	--	--	--	--	--	--	No	No
O'Brien 2002	Regional mCSCC with parotid gland involvement	87	72 (37-88)	77 (89)	--	12 (14)	75 (86)	--	--	--	--	--	--	0 (0)	0 (0)	0 (0)	No	No
Retrospective studies																		
Amoils 2017	Regional mCSCC	80	73	71 (89)	--	13 (16)	36 (45)	31 (39)	--	--	--	--	15 (19)	--	--	--	Yes	No
Andruchow 2006	Regional mCSCC with parotid gland or neck lymph node involvement	322	68 (28-98)	239 (74)	--	55 (17)	236 (73)	--	31 (10)	--	--	--	--	0 (0)	0 (0)	0 (0)	No	No
Audet 2004	Regional mCSCC	56	76 (49-97)	43 (77)	--	7 (13)	37 (66)	--	12 (21)	56 (100)	0 (0)	0 (0)	--	--	--	--	No	No
Beydoun 2012	Regional mCSCC	36	75 (36-92)[b]	27 (75)	0: 14 (39) 1: 13 (36) 2: 9 (25)	--	26 (72)	--	10 (28)	5 (14)	14 (39)	10 (28)	1 (3)	--	--	--	Yes	No
Bova 2004	Patients who underwent parotidectomy	34	--[c]	--	--	4 (12)	30 (88)	--	--	--	--	--	--	--	--	--	No	No
Bron 2003	Parotid cancers: primary cancer, and cancers secondary to mCSCC	101	--[c]	--	--	15 (15)	86 (85)	--	--	--	--	--	--	--	--	--	No	No
Ch'ng 2006	Regional mCSCC	58	71[b]	46 (79)	--	19 (33)	39 (67)	--	--	55 (98)	--	--	7 (12)	--	--	--	Yes	No
Ch'ng 2008	Regional mCSCC	170	74 (32-96)[b]	146 (86)	--	39 (23)	131 (77)	--	--	149 (88)	--	--	--	--	--	--	Yes	No
Coombs 2017	Regional mCSCC	63	72 (44-92)[b]	53 (84)	--	12 (19)	51 (81)	--	--	≥33 (52)	--	--	--	--	--	--	No	No
delCharco 1998	mCSCC, undifferentiated carcinoma, metatypical basal cell carcinoma	72	68 (28-103)[b]	70 (91)	--	24 (31)	53 (69)	--	--	--	--	--	--	--	--	--	Yes	No

Study	Population	N	Age, median (range)	Male	ECOG PS	Intervention groups				Primary tumour site			Immuno-compromised	Prior treatment experience			KM curves	
						Sx alone	Sx + adj. RT	Sx + adj. CRT	RT alone	H&N	Trunk	Extremities		Sx	RT	CT	OS	PFS
Dona 2003	Regional mCSCC	74	65 (34-93)	63 (85)	--	--	74 (100)	--	--	(89)	--	--	3 (4)	--	--	--	Yes	No
Ebrahimi 2012	Regional mCSCC	168	72 (37-89)	142 (85)	--	33 (20)	135 (81)	--	--	168 (100)	0 (0)	0 (0)	2 (1)	--	--	--	No	No
Ebrahimi 2013	Regional mCSCC	229	68 (18-95)	187 (82)	--	28 (12)	196 (86)	5 (2)	--	229 (100)	0 (0)	0 (0)	19 (8)	--	--	--	No	No
Forest 2010	Regional mCSCC	215	73 (25-94)	188 (87)	--	40 (19)	158 (74)	17 (8)	--	215 (100)	0 (0)	0 (0)	5 (2)	--	--	--	Yes	No
Givi 2011	Regional mCSCC	51	73 (43-90)	47 (92)	--	11 (22)	40 (78)	--	--	51 (100)	0 (0)	0 (0)	11 (22)	--	--	--	Yes	No
Hinerman 2008	Regional mCSCC with parotid gland involvement	117	67 (28-103)	108 (92)	--	--	104 (86)	--	17 (14)	117 (100)	0 (0)	0 (0)	--	--	--	--	Yes	No
Hong 2005	Parotid bed lymph node metastases arising from a prior CSCC	20	--	16 (80)	--	6 (30)	14 (70)	--	--	20 (100)	0 (0)	0 (0)	--	--	--	--	No	No
Iyer 2009	Regional mCSCC with parotid gland involvement	176	72.5 (38-100)	159 (90)	--	38 (22)	138 (78)	--	--	--	--	--	--	--	--	--	Yes	No
Jol 2002	Regional mCSCC	41	74.3 (40-92)[b]	26 (63)	--	9 (22)	24 (59)	--	8 (20)	41 (100)	0 (0)	0 (0)	--	--	--	--	Yes	No
Joseph 1992	Regional mCSCC	34	--	30 (88)	--	21 (62)	--	--	13 (38)	0 (0)	7 lesions	27 lesions	--	--	--	--	No	No
Khurana 1995	Regional mCSCC	75	67 (32-88)	69 (92)	--	18 (24)	50 (67)	--	7 (9)	75 (100)	0 (0)	0 (0)	--	--	--	--	No	No
Kirke 2011	Regional mCSCC	51	69 (42-91)	45 (88)	--	10 (20)	41 (80)	--	--	12 (24)	--	--	--	--	--	--	Yes	No
Kosec 2013	Regional mCSCC	24	--	12 (50)	--	24	--	--		24 (100)	0 (0)	0 (0)	--	--	--	--	Yes	No
Kraus 1998	Regional mCSCC	45	67 (37-85)[b]	38 (84)	--	9 (20)	36 (80)	--	--	45 (100)	0 (0)	0 (0)	4 (9)	--	--	--	Yes	No
McDowell 2016	Regional mCSCC with parotid gland involvement	132	76 (27-98)	121 (92)	--	--	105 (80)	27 (21)	--	132 (100)	0 (0)	0 (0)	33 (25)	--	--	--	Yes	No
Oddone 2009	Regional mCSCC	250	67 (34-95)	207 (83)	--	28 (11)	222 (89)	--	--	≥69 (37)	--	--	15 (6)	--	--	--	Yes	No
Palme 2003	Regional mCSCC	123	69 (24-100)	104 (83)	--	12 (10)	93 (74)	--	18 (14)	--	--	--	18 (14)	0 (0)	0 (0)	0 (0)	No	No
Schmidt 2015	Regional mCSCC	113	74 (41-93)	93 (82)	--	13 (12)	100 (89)	--	--	113 (100)	0 (0)	0 (0)	12 (11)	--	--	--	Yes	No
Shao 2014	Regional mCSCC	160	--	132 (83)	--	32 (20)	128 (80)	--	--	--	--	--	28 (18)	8 (5)	22 (14)	--	No	No

Study	Population	N	Age, median (range)	Male	ECOG PS	Intervention groups				Primary tumour site			Immuno-compromised	Prior treatment experience			KM curves	
						Sx alone	Sx + adj. RT	Sx + adj. CRT	RT alone	H&N	Trunk	Extremities		Sx	RT	CT	OS	PFS
Southwell 2006	Regional mCSCC	49	72 (51-90)[b]	(88)	--	13 (27)	36 (74)	--	--	--	--	--	9 (18)	9 (18)	10 (20)	--	Yes	No
Veness 2003	Regional mCSCC with involvement of the cervical (non-parotid) lymph nodes	74	66 (37-93)	59 (80)	--	13 (18)	52 (70)	--	9 (12)	74 (100)	0 (0)	0 (0)	2 (2.8)	--	--	--	Yes	No
Veness 2005	Regional mCSCC with parotid gland or neck lymph node involvement	167	67 (34-95)	143 (86)	--	21 (13)	146 (87)	--	--	167 (100)	0 (0)	0 (0)	10 (6)	--	--	--	Yes	No
Wang 2012	Regional mCSCC	122	66 (18-95)	94 (77)	--	20 (16)	102 (84)	--	--	122 (100)	0 (0)	0 (0)	8 (7)	0 (0)	0 (0)	0 (0)	Yes	No
Wang 2013B	Regional mCSCC	122	66 (18-95)	49 (74)	--	20 (16)	102 (84)			122 (100)	0 (0)	0 (0)	8 (7)	0 (0)	0 (0)	0 (0)	Yes	No
Cross-sectional studies																		
Wang 2013A	Regional mCSCC	42	71[b]	35 (83)	--	3 (7)	27 (64)	11 (26)	1 (2)	42 (100)	0 (0)	0 (0)	2 (5)	--	--	--	No	No

Notes: *All values are reported as n (%) unless specified otherwise.* ***a)*** *Population was a mix of patients with mCSCC (n=40) and patients with local disease who underwent local resection (n=153); patient characteristics are presented for the former group which is of interest;* ***b)*** *Mean was reported;* ***c)*** *Not reported for the CSCC subpopulation.* ***Abbreviations:*** *CRT, chemoradiotherapy; CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck; KM, Kaplan-Meier; mCSCC, metastatic CSCC; OS, overall survival; PFS, progression-free survival; PS, performance score; RT, radiotherapy; Sx, surgery.*

Table 2: Summary of the 16 comparator studies featuring systemic interventions

Study	N	Intervention	Population			Age, median (range)	Male	ECOG PS				Primary tumour site [a]			Immuno-compromised	Prior treatment experience			KM curves	
			laCSCC	mCSCC				0	1	2	3	H&N	Trunk	Extremities		Surgery	RT	CT	OS	PFS
				Regional	Distant															
Phase II single-arm clinical trials																				
Bossi 2017	42	Dacomitinib	12 (29)	19 (45)	11 (26)	77 (45-91)	34 (79)	24 (57)	17 (40)	1 (3)	0 (0)	28 (67)	3 (7)	11 (26)	9 (21)	35 (83)	21 (50)	6 (14)	Yes	Yes
Gold 2018	39	Erlotinib	0 (0)	39 (100)		65 (45-88)	34 (87)	11 (28)	23 (59)	5 (13)	0 (0)	31 (79)	3 (8)	5 (13)	--	38 (97)	32 (82)	16 (41)	Yes	Yes
Foote 2014	16	Panitumumab	0 (0)	13 (81)	3 (19)	68 (47-86)	14 (88)	2 (13)	12 (75)	2 (13)	0 (0)	--			--	12 (75)	14 (87)	7 (43)	Yes	Yes
Lippman 1992	28	13-cis-retinoic acid + IFNα	14 (50)	6 (21)	8 (29)	67 (49-88)	26 (93)	Median (range): 1 (0-2)			0 (0)	19 (68)	1 (4)	8 (29)	--	26 (92.9)	18 (64)	6 (21)	No	No
Maubec 2011	36	Cetuximab	17 (47)	16 (44)	3 (8)	79 (32-95)	21 (58)	11 (31)	17 (47)	8 (22)	0 (0)	5 (14)	17 (47)	14 (39)	0 (0)	19 (52)	9 (25)	0 (0)	Yes	Yes
Nottage 2017	21	Cisplatin + RT	5 (24)	16 (76)	0 (0)	62 (36-84)	18 (86)	20 (95)[b]		1 (5)	0 (0)	20 (95)	0 (0)	1 (5)	1 (4.8)	--	--	--	Yes	Yes
Preneau 2014	9	Cetuximab + carboplatin	16 (80)	4 (20)	0 (0)	76 (50-86)	9 (100)	--				5 (56)	1 (11)	3 (33)	1 (11.1)	6 (66.7)	5 (56)	--	No	No
	6	Cetuximab				69.5 (51-91)	3 (50)					4 (67)	0 (0)	2 (33)	3 (50)	6 (100)	3 (50)	--		
	5	Cetuximab + RT				77 (62-86)	3 (60)					4 (80)	0 (0)	1 (20)	1 (20)	5 (100)	0 (0)	--		
William 2017	40	Gefitinib	4 (10)	27 (68)	9 (23)	67 (37-95)	30 (75)	4 (10)	32 (80)	4 (10)	0 (0)	32 (80)	2 (5)	6 (15)	--	35 (88)	33 (83)	18 (45)	Yes	Yes
Prospective case series																				
Sadek 1990	14	Cisplatin + 5-FU + bleomycin	5 (35.7)	9 (64.3)	0 (0)	59 (7-80)	11 (79)	--				14 (100)	0 (0)	0 (0)	--	8 (53.3)	4 (27)	1 (7)	No	No
Retrospective observational studies																				
Beasley 2017	18	Nivolumab or pembrolizumab	8 (44)	5 (28)	3 (17)	77 (55-91)	10 (56)	--				--				18 (100)	12 (67)	--	No	No
Dereure 2017	10	Cetuximab	5 (50)	3 (30)	2 (20)	72.5 (18-92)	13 (93)	--				9 (64)	5 (36)	--	1 (7.1)	11 (79)	9 (64)	3 (21)	No	Yes
	4	Cetuximab + carboplatin	2 (50)	0 (0)	2 (50)															
Di Monta 2017	22	ECT with bleomycin	22 (100)	0 (0)	0 (0)	72 (51-88)	15 (68)	--				16 (73)	1 (5)	5 (23)	--	--	--	--	No	No
Guthrie 1990	12	Cisplatin + doxorubicin	9 (75)	3 (25)		66.5 (58-78)	9 (75)	--				7 (58)	--	3 (25)	--	10 (83)	4 (33)	--	No	No

Study	N	Intervention	Population			Age, median (range)	Male	ECOG PS				Primary tumour site [a]			Immuno-compromised	Prior treatment experience			KM curves	
			laCSCC	mCSCC				0	1	2	3	H&N	Trunk	Extremities		Surgery	RT	CT	OS	PFS
				Regional	Distant															
Jarkowski 2016	25	Chemotherapy	19 (76)	6 (24)		66.4 (2.8)[b]	18 (72)	--				11 (44)	7 (28)	3 (12)	--	--	--	8 (32)	Yes	Yes
Picard 2017	31	Cetuximab	12 (39)	13 (42)	6 (19)	86 (48-96)	22 (71)	5 (16)	15 (48)	9 (29)	2 (7)	22 (71)	3 (10)	6 (19)	15 (48)	23 (74)	15 (48)	3 (10)	Yes	No
Samstein 2014	12	Cetuximab + RT	4 (33)	6 (50)	2 (17)	78 (47-90)	11 (92)	--				--			5 (42)	-- (82)	--	0 (0)	Yes	Yes

Notes: *All values are reported as n (%) unless specified otherwise.* ***a)*** *Values were calculated if individual tumour sites (e.g. ear, face, hand) were reported;* ***b)*** *Mean (standard deviation) was reported.* ***Abbreviations:*** *CRT, chemoradiotherapy; CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; H&N, head and neck; KM, Kaplan-Meier; mCSCC, metastatic CSCC; OS, overall survival; PFS, progression-free survival; PS, performance score; RT, radiotherapy.*

Table 3: Summary of tumour grade, perineural invasion, and tumour size across the studies reporting at least one of these characteristics

Study	N	Tumour differentiation grade				Tumour size/depth	Perineural invasion
		G1	G2	G3	G4		
Amoils 2017	80	6 (7)	37 (46)	18 (22)	20 (25)	Size >2cm: 11 (14%)	33 (41)
Audet 2004	56	--				--	13 (23)
Beydoun 2012	36	--	13 (36)	13 (36)	--	--	--
Dereure 2017	14	6 (43)	8 (57)	0 (0)	0 (0)	--	--
Di Monta	22	12 (55)	8 (15)	2 (14)	--	--	--
Dona 2003	74	--	(70)		--	--	--
Ebrahimi 2012	168	--	--	47 (28)	--	--	15 (9)
Ebrahimi 2013	229	151 (66)		78 (34)		Size: • ≤2cm: 117 (51) • >2cm: 55 (24) Depth: • ≤5mm: 58 (25) • >5mm: 61 (27)	32 (14)
Givi 2011	51	2 (5)	21 (52)	17 (42)	--	--	19 (37)
Hinerman 2008	117	--				--	23 (20)
Jol 2002	41	--				--	6 (15)
Joseph 1992	34	8 (24)	7 (21)	7 (21)	--	--	
Khurana 1995	75	--	--	32 (43)	--	--	12 (16)
Kosec 2013	24	--				Size >2cm: 24 (100)	--
Kraus 1998	45	--				Size: • >2cm: (81) • Mean: 2.9cm Depth: • >4mm: (83) • Mean: 1cm	--
McDowell 2016	132	4 (3)	40 (34)	75 (63)	--	--	38 (29)
Moore 2005	40	--	--	13 (33)	--	Mean size: 4.2cm Mean depth: 15.4mm	16 (40)
Oddone 2009	250	--				Median size: 15mm Median depth: 6 mm	--
Picard 2017	31	15 (48)	8 (26)	7 (23)	--	--	--
Wang 2012	122	--	60 (49)		--	--	--

Notes: *All values are reported as n (%) unless specified otherwise.* ***Abbreviations:*** *G1, well-differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated.*

A3. Priority question. The consideration of relevant comparators in section B.2.9.1 and in Appendix D does not explicitly discuss whether any of the identified studies could have provided any relevant data on BSC. Please clarify whether any studies have control arms or subgroups that could be relevant? (e.g. non-platinum-treated patients in the Jarkowski study or other studies?). Were any

of the excluded studies of surgery in populations that might serve as surrogates for BSC?

In the case of Jarkowski 2016, only 7 patients did not receive platinum based chemotherapy, but all these patients either received alternative chemotherapies (capecitabine or taxanes) and/or targeted therapy with cetuximab. Given the small sample size and uncertainty over whether these patients received chemotherapy or not, we do not believe these could be used as a surrogate for BSC. In the remaining studies of systemic therapies which did not feature chemotherapy, it is clear from **Table 2** above that none of the intervention profiles correspond to BSC as they assess treatments with a non-palliative intent.

In terms of the surgery studies, patients generally received curative surgical interventions with or without radiotherapy (see response to question A2 above); examples of those surgical interventions included resection of cervical lymph nodes at various levels (e.g. selective or modified radical neck dissection) and/or various levels of parotidectomy (i.e. superficial, radical, or total) in addition to complete resection of the primary tumour (with clear or close margins) if present. These patients therefore do not correspond to the population of interest and as a result could not be used as a surrogate for BSC.

Given the paucity of data on the efficacy and safety of BSC in advanced CSCC, as discussed in section B.3.3.2.6., a conservative assumption was made in the base case to use the extrapolated PFS and OS curves based on the chemotherapy data as a proxy for BSC. However, in sensitivity analyses, data from studies of EGFR inhibitors were used as an alternative proxy for BSC on the basis that these therapies were not expected to be effective in CSCC according to clinical opinion sought in a UK advisory board organised by Sanofi. Both of these approaches were discussed during the advisory board and were considered reasonable by clinical experts in the absence of more robust evidence for BSC. Sanofi is currently conducting a retrospective chart review study, expected to report in 2019, which is anticipated to reduce the uncertainty around the efficacy associated with the current standard of care. Sanofi propose that data generated by the retrospective chart review be incorporated into the data collection agreement (DCA) were cemiplimab to be recommended for use via the CDF.

A4. **Priority question. Median follow-up was 11.1 months (range 1.1 to 17) in the phase I study (section B.2.3.1), 8.6 months (range 0.8 to 15.9) in EMPOWER-CSCC (section B.2.3.2), and 8.56 months (0.8-15.9 months) for the integrated analysis (section B.2.4).**

(a) Please explain why the follow-up in the integrated analysis is shorter than for either of the constituent studies.

Apologies, this was reported incorrectly in our evidence submission. The median duration of follow-up for the integrated analysis was 8.92 months (0.8-17.0 months).

(b) Please explain how the minimum follow-up can be 0.8 months in the EMPOWER-CSCC study and 1.1 months in the phase I study if there are no patients in either study with follow up <9 months?

The analysis for the metastatic CSCC group included patients who had the opportunity for exposure to cemiplimab for ≥6 months (i.e., initiated treatment at least 6 months before data cut-off). The analysis for locally advanced CSCC included patients who had an opportunity for exposure to cemiplimab for ≥9 months (i.e., initiated treatment at least 9 months before data cut-off). Although all patients had the opportunity for durable follow up, some patients discontinued early (e.g., disease progression, death, etc.) and therefore had shorter follow-up on study.

(c) Please provide the median (range) follow-up for the laCSCC and mCSCC subgroups in each study. For the laCSCC subgroup in the EMPOWER-CSCC study please provide the length of follow-up (i) including the 32 patients who had follow-up less than 9 months and (ii) excluding the 32 patients who had follow-up less than 9 months.

The median follow-up for the laCSCC and mCSCC subgroups in the phase I and the phase II studies be found in **Table 4** and **Table 5** respectively.

Table 4: Median follow up for laCSCC and mCSCC subgroups in the phase I study

Study/Analysis	mCSCC	laCSCC
Phase I study	[redacted]	[redacted]

Notes: ** Duration of follow-up in the phase I study was not stratified for the safety and efficacy analysis sets.*

Table 5: Median follow up for laCSCC and mCSCC subgroups in the phase II study

Study/Analysis		mCSCC		laCSCC
		3 mg/kg q2w	350 mg q3w	3 mg/kg q2w
Phase II study	Safety analysis	[redacted]	[redacted]	[redacted]
	Efficacy analysis	[redacted]	[redacted]	[redacted]

In addition, in **Table 6**, the length of follow-up for the laCSCC subgroup in the phase II, EMPOWER-CSCC study, including the 32 patients who had follow-up less than 9 months and excluding the 32 patients who had follow-up less than 9 months, is provided.

Table 6: Median follow up for the laCSCC subgroup in phase II study including and excluding patients who had follow-up less than 9 months

Study/Analysis		laCSCC
Phase II study	**Including** patients with <9 months follow-up (same as safety analysis)	[redacted]
	Excluding patients with <9 months follow-up (same as efficacy analysis)	[redacted]

(d) Please provide the median (range) follow-up for the non-CSCC patients in the phase I study (to assist the ERG to interpret the safety data).

The median duration of follow-up for the non-CSCC patients in the phase I study was [redacted] months with a range of [redacted].

A5. Table 5 in section B.2.3.2.2 reports the baseline characteristics for the full EMPOWER-CSCC study (i.e. groups 1+2+3; n=137). Please provide the baseline characteristics for the subgroup from the EMPOWER-CSCC study included in the FAS (i.e. n=82).

The baseline characteristics for the FAS from the phase II, EMPOWER-CSCC study can be found in **Table 7**.

Table 7: Baseline characteristics, phase II EMPOWER-CSCC 1 (Full Analysis Set)

	Phase II EMPOWER-CSCC 1 (N=82)
Male, n (%)	[redacted]
Median age (range)	[redacted]
Weight, mean kg (SD)	[redacted]
ECOG PS, n (%)	[redacted]
Prior cancer related systemic therapy, n (%)	[redacted]
No. of regimens at baseline, n (%) 0 1 ≥2	[redacted]
Prior cancer related surgery, n (%)	[redacted]
Prior cancer related RT, n (%)	[redacted]

A6. Please provide the reference and PDF, including any supplemental material, for the review by Yanagi et al 2018 which is referred to in section D.1.2.1.

This PDF for this study has been attached to this response.

Identification of prognostic factors for CSCC

A7. Please provide the references and PDFs for the 28 studies of prognostic factors for CSCC that are summarised in Appendix D.1.3.3

The full list of references can be found below and the corresponding PDFs have been attached separately:

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.
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A8. Please explain how the results of the search were "validated by consulting clinicians…" as stated in section B.2.9.1.1, and the number of clinicians that were consulted.

Prognostic factors were validated by oncologists and dermatologists participating in the experts' elicitation exercise. The design and setting of the interviews have been explained in more detail in Appendix M. The 11 experts who participated 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 8**. Overall, the experts generally agreed with the list of identified prognostic factors. The only additional prognostic factors suggested by expert 1 were [redacted] which were not reported in Jarkowski 2016.

Table 8: 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]

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 10	[redacted]	[redacted]
Expert 11	[redacted]	[redacted]

A9. Please explain the format of Table 8 in Appendix D, as this is not fully intuitive. Do the numbers reported in columns 3-6 refer to the number of studies? What is the difference between "Reported" and "Significant"? What does "Data availability in studies included in the analysis" mean? Please indicate which studies provided the data that are shown in each cell of the table, as these data cannot be traced to specific studies.

Columns 3 to 6 in Table 8 of Appendix D refer to the number of studies that investigated the effect of potential prognostic factors on survival (in the "Reported" column) and the number of studies that found that effect to be statistically significant (in the "Significant" column). In the last column ("Data availability in studies included in the analysis"), the number of studies reporting on each identified factor is presented. For example, of the seven studies that were included in the analysis, four reported on immune status and none reported on perineural invasion. **Table 9** below provides additional detail regarding which patient/tumour characteristics were investigated across the prognostic studies, and presents the list of prognostic factors that were found to have a statistically significant influence on survival outcomes in each study.

Table 9: Summary of the patient/tumour 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	Tumour grade (for disease-free survival)	Tumour 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	Tumour grade	Tumour grade	--	--
Carter 2013	Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: An 11-year cohort study	Age, gender, nerve caliber, tumour diameter <2cm, tumour grade, depth of invasion (beyond subcutaneous fat), number of nerves involved, vascular/lymphatic invasion	Age, tumour diameter <2cm, vascular or lymphatic invasion, depth of invasion (dermis/subcutaneous fat vs. invasion beyond subcutaneous fat)	--	--
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; tumour size >2cm; higher expression level for p300 (poorer OS)	Scalp or neck (poorer 5-year OS rate) vs. ear or lip; tumour 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	--	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
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	--	--
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, tumour grade, number of positive nodes	--	Immune suppression, perineural invasion, extracapsular extension, degree of tumour differentiation (grade), number of positive nodes	--
Gonzalez-Guerrero 2017	The adverse prognostic effect of tumour budding on the evolution of cutaneous head and neck squamous cell carcinoma	Tumour budding	--	--	--
Hinerman 2008	Cutaneous squamous cell carcinoma metastatic to parotid-area lymph nodes	--	--	Tumour grade, perineural invasion, P stage, N stage, extracapsular spread (all for disease-free survival)	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
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)	--	--
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), tumour 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	--	--	Tumour 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	Tumour grade, tumour stage, CD200 expression, gender, tumour size, age	Tumour grade, stage, CD200 expression	--	--
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
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	--

Study	Title	Overall survival		Progression-free survival	
		Investigated factors	Significant factors	Investigated factors	Significant factors
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	--	--
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, tumour diameter <2, tumour grade, tumour depth, perineural invasion, lymphovascular invasion, tumour location (head and neck, ear, …)	Tumour depth and tumour grade	--	--
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)
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, tumour/node/metastasis staging system.*

A10. Figure 7 in section B.2.3.1.3 indicates that data should be available for 23 patients who received cemiplimab 350 mg q3w. Please provide clinical effectiveness outcomes for OS, PFS, ORR and DOR for these patients. If possible, please also provide the baseline characteristics for these patients.

At the time of the 27 October 2017 data cut-off, there was limited follow-up for patients enrolled in Group 3 (mCSCC, 350mg q3w) of the phase II, EMPOWER-CSCC study. The median duration of follow-up for these patients was [redacted]. This was not adequate follow-up for measurement of response, and there is no centrally reviewed data available.

The baseline characteristics for the 23 patients enrolled in Group 3 (350mg q3w) of the phase II, EMPOWER-CSCC study as of 27 October 2017 are reported in **Table 10**.

Table 10: Baseline characteristics of patients in Group 3 (mCSCC, 350mg q3w), phase II EMPOWER-CSCC 1

	mCSCC Cemiplimab: 350 mg Q3W (N=23)
Male, n (%)	[redacted]
Median age (range)	[redacted]
Weight, mean kg (SD)	[redacted]
ECOG PS, n (%)	[redacted]
Prior cancer related systemic therapy, n (%)	[redacted]
No. of regimens at baseline, n (%) 0 1 ≥2	[redacted]
Prior cancer related surgery, n (%)	[redacted]
Prior cancer related RT, n (%)	[redacted]

Data collection is ongoing. We anticipate that a new data cut will be available for us to share at the time of the technical consultation.

A11. Priority question. The matching employed in the MAIC and STC analyses assumes by default that the Jarkowski study is the "real world" target population relevant to this technology appraisal. This is a critical assumption but the study is very small (25 participants), retrospective (so at risk of bias) and few details of the population are reported. Please explain why a better estimate of the target population has not been provided. Could the retrospective chart review referred to in section B.2.11 provide a more relevant target population? Please provide the details of the chart review population.

As discussed in section B.2.1. a full systematic literature review (SLR) was performed to identify studies that investigated the efficacy and safety of treatments for patients with advanced CSCC, the target population for this submission. After excluding studies not relevant to the decision problem in the UK, there was only one study by Jarkowski and colleagues, which included patients who received platinum-based chemotherapy, which was deemed relevant and therefore was included in the indirect as well as the naïve comparisons versus cemiplimab.

Given the limited available evidence on advanced CSCC in the public domain as well as the challenges in identifying advanced CSCC patients in many registries and national databases this was deemed to be the most relevant data that can be used for comparative purposes at the time of this submission. Despite its limitations, this approach was further validated with UK clinicians during an advisory board organised by Sanofi who also confirmed the scarcity of the data on advanced CSCC patients.

The retrospective chart review study, conducted by Sanofi, is currently ongoing as patients that match the criteria for inclusion are still being recruited in the US and EU, including the UK. The study has been designed to be reflective of the advanced CSCC population addressed in our submission. Inclusion and exclusion criteria are provided in **Table 11**. Sanofi agree that the scarcity of available data on the target population is a key limitation of our submission and also agree that once available the results of the chart review should provide a more appropriate dataset to base

comparisons on. Sanofi will make NICE aware if any data from this study become available during the appraisal process for cemiplimab.

Table 11: Inclusion and exclusion criteria applied for the retrospective chart review study

Inclusion Criteria
Inclusion Criteria – All Cohorts
• Adults 18 years of age or older at mCSCC or laCSCC diagnosis • Diagnosis of mCSCC or laCSCC occurring between January 1, 2011 and December 31, 2015 • Documented pathologic confirmation of mCSCC or laCSCC (i.e., biopsy confirmed) • CSCC medical history is available from mCSCC or laCSCC diagnosis within the medical record for abstraction
Inclusion Criteria – mCSCC Cohort 1
• Patients with metastatic lesions at index date* (local/regional nodal and/or distant). Local/regional refers to lymphatic metastasis to local/regional lymph node. Distant refers to distant nodal involvement or visceral lesion such as lung, liver or bone.
Inclusion Criteria – laCSCC Cohort 2
• Patients with locally advanced disease and no evidence of metastases (e.g. M0 patients) at index date* are included if they meet criteria "a" and **either** criteria "b" or "c": – a. no evidence of additional surgery or radiation for recurrent CSCC in the same location during study period; AND b. if they use any systemic therapy for non-curative intent; systemic (IV or oral) therapies include chemotherapy, EGFR, other systemic agents OR c. no evidence of additional treatment (e.g., best supportive care)
Exclusion Criteria
Exclusion Criteria- All Cohorts
• Enrolled in a clinical trial related to CSCC therapy since mCSCC or laCSCC diagnosis • Squamous cell carcinoma of the mucous membranes, of the head and neck (i.e., eyes, inside ears, inside nose, inside mouth or throat, lung, or anogenital region) • Immunocompromised or immune suppressed at the time of mCSCC or laCSCC diagnosis • SCC of unknown primary
Exclusion Criteria- laCSCC Cohort 2
• Patients receiving surgeries for target lesion during study period; this does NOT pertain patients who receive surgeries for minor or non-target lesion, or for palliative (non-curative) intent • Patients receiving radiation therapy for target lesion during study period; this does NOT pertain to patients who receive radiation therapy for minor or non-target lesion • Confirmatory evidence of metastases, e.g., radiologic imaging, chest imaging, ALT/AST elevation in the absence of radiologic scan within 3 months suggesting liver metastasis *[Note: Please move to cohort 1 if patients have evidence of metastasis with radiologic scan within 3 months.]* • Use of topical chemotherapy, e.g., topical 5-FU or chemoprevention agents such as nicotinamide during study period for target lesion

**Note, Index date is defined as first mCSCC or laCSCC diagnosis date*

A12. Section B.2.9: Please provide the weights given to each patient in the MAIC. We are interested in whether certain patients are driving the analysis and how they correspond to the real-world population.

A graphical representation of the weights used in the MAIC by time to event for overall survival are presented in Figure 1. As discussed in section B.2.9.3.1 of our submission, the results of the MAIC were mainly driven by six patients who received disproportionately higher weights than the rest of the sample, with the effective sample size also being reduced by 65.7% to n=37. All these patients had laCSCC and all but one had lesions located on the extremities (Table 12

Table 12). This is understandable as there were lower proportions of laCSCC patients [redacted] and those with lesions not located on their head and neck [redacted] in the pooled data from the cemiplimab studies compared to Jarkowski 2016. The fact that the results of the MAIC were being driven by such a small number of patients was major factor in our decision to use the results of the STC as a key alternative scenario analysis within the cost-effectiveness modelling. However, given the uncertainties surrounding both of the indirect comparisons performed, as discussed in section B.2.9.4., the naïve (unadjusted) comparison was used in the base case analysis as this provided the most conservative estimates of differences in treatment effects.

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Figure 1: Weights used in matching-adjusted indirect comparisons of cemiplimab versus chemotherapy with platinum using Jarkowski 2016 by time to event (overall survival)

[redacted]

Table 12: Characteristics of six patients who received disproportionately higher weights in matching-adjusted indirect comparison

Weight	Age	Country	Disease stage	Primary tumour site	T Stage	ECOG PS	Prior systemic therapy	Prior radiotherapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced CSCC; PS, performance score.*

A13. Section B.2.3.1.3 states that 32 participants from the EMPOWER-CSCC study were excluded from the FAS as they did not complete at least 9 months follow-up (to allow minimum duration of response of 6 months as per FDA

recommendation). Please provide an analysis, with the HR or OR and confidence interval where appropriate, that includes these 32 patients for the outcomes specified in the decision problem (OS, PFS, ORR, DOR):

(a) For the integrated analysis FAS (i.e. n=140).

(b) For the integrated analysis laCSCC subgroup (i.e. n=65) and for the EMPOWER-CSCC study laCSCC subgroup (n=55).

At the time of the data cut-off, these 32 patients did not meet the required duration of follow-up (as pre-specified in the interim analysis) for efficacy/response evaluation. Therefore, there is no centrally reviewed efficacy data available for these patients. Also, the only efficacy analysis that was performed for the laCSCC subgroup was for the 23 patients with sufficient follow-up at time of FAS.

Data collection is ongoing. We anticipate that a new data cut will be available for us to share at the time of the technical consultation.

A14. For Table 10 in Appendix D.1.3.5 please provide definitions for the core model and the different extended models, and which covariates were included in each, as these models are not fully explained in section B.2.9.2.3.

Covariates included in the core model for the analysis were those reported as statistically significant in at least one study identified in the targeted literature review of prognostic factors: immune status (note immunocompromised patients were excluded from the cemiplimab trials), age, disease stage, tumour grade, perineural invasion, tumour size, tumour depth, and tumour location. Of these, only disease stage and tumour location were reported in the Jarkowski study and therefore could be adjusted for in the analyses (note the fit between this model and the full core model were comparable). Note that given how similar the two cemiplimab studies were in terms of inclusion criteria and patient characteristics, it was not necessary to include a study-level factor in the model (this was explored and was found not to improve the overall fit). Additional covariates included in an extended model were those that were not found to be significant or those that had not been studied in

CSCC but had been found to be relevant in other tumour types: gender, ECOG performance score, prior systemic therapy, and prior radiotherapy.

A15. Section B.2.9.2.3 states that the coefficients for the extended models differed in a direction contrary to what was expected. Please provide the covariates and their coefficients.

A1. As noted in the response to question A14, the core and extended model for the comparison with chemotherapy differed slightly from the global models, as not all covariates were reported in the Jarkowski 2016 study. The coefficients from the two models as fitted in this comparison are presented in **Table 13**, **Table 14**, and **Table 15** for OS, PFS, and ORR, respectively.

A2.

A3. **Figure** 2, **Figure 3**, and

Figure 4 show predicted outcomes for cemiplimab when using the two models for the three outcomes. In all cases the core model provided a similar or more conservative estimate than the extended model, with no substantial differences in overall model fit (in the case of PFS the core model was the slightly better fitting model). Based on this and also the small sample size (n=18) of the Jarkowski 2016 study, results from the more parsimonious core model were deemed the most appropriate of the two for use within the economic model.

Table 13: Coefficients from core and extended models for overall survival

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]
Prior systemic therapy (yes vs no)	--	--	[redacted]	[redacted]
AIC	[redacted]		[redacted]	

Abbreviations: *AIC, Akaike Information criterion; HR, hazard ratio; SE, standard error.*

Table 14: Coefficients from core and extended models for progression-free survival

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]
Prior systemic therapy (yes vs no)	--	--	[redacted]	[redacted]
AIC	[redacted]		[redacted]	

Abbreviations: *AIC, Akaike Information criterion; HR, hazard ratio; SE, standard error.*

Table 15: Coefficients from core and extended models for objective response

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]
Prior systemic therapy (yes vs no)	--	--	[redacted]	[redacted]
AIC	[redacted]		[redacted]	

Abbreviations: *AIC, Akaike Information criterion; HR, hazard ratio; SE, standard error.*

Figure 2: Unadjusted and population-adjusted Kaplan-Meier curves for overall survival with cemiplimab overlaid with observed curve for chemotherapy with platinum from Jarkowski 2016

Figure 3: Unadjusted and population-adjusted Kaplan-Meier curves for progression-free survival with cemiplimab overlaid with observed curve for chemotherapy with platinum from Jarkowski 2016

Figure 4: Unadjusted and population-adjusted response rates with cemiplimab compared with observed response for chemotherapy with platinum from Jarkowski 2016

A16. Appendix D.1.3.6 briefly mentions the programming language for the STC and MAIC analyses. Please provide the full R statistical code used for these analyses, together with the IPD data used in the model for the cemiplimab and Jarkowski studies.

The R code used to conduct the statistical analyses has been attached to this response. Unfortunately Sanofi are not able to provide the IPD data, however, Sanofi are willing to conduct any further analyses requested by the ERG.

A17. Did the company assess the proportional hazards assumption for OS and PFS in the MAIC analysis? The submission states above Fig 23 (section B.3.3.2.1) that the proportional hazard (PH) assumption was not expected to be valid. However, results of a PH test are reported in Fig 23 and the company submission reports constant hazards as the output from the matching analysis. Please explain how PH were assessed for each relevant comparison (what test does the p-value reported in Figure 23 refer to?). If the PH assumption was not satisfied please explain the implications of this for interpreting the results?

We assessed proportionality in comparisons across therapies as well as across strata within the cemiplimab trials for which IPD were available, where strata were defined by covariate values. The proportional hazards assumptions were assessed using the cox.zph function, which assesses proportionality by examining the

correlation between the Schoenfeld residuals and time. Assessments of proportionality were made for each of the comparators of interest, and none showed a violation of this assumption. However, these assessments may be underpowered given the relatively small sample. Similarly, across strata the proportionality assumption was not violated, which justified the use of proportional hazard models for the STC and MAIC. Again, however, some strata were limited in size. Despite the above, our expectation was that assuming proportional hazards for the purposes of the economic model would not be appropriate. This assumption was based on the different mode of action of PD-1 inhibitors compared to chemotherapy and also previous submissions for these therapies which have shown this to be the case.

A18. The EGFR inhibitors cetuximab, gefitinib and erlotinib are included as overlaid observed data in the MAIC/STC analysis results in section D.1.3.5. Given that these therapies are outside of the NICE scope and the company's decision problem, the rationale for these comparisons is unclear. Please provide an explanation for these naïve unanchored comparisons of cemiplimab against the EGFR inhibitors.

Although EGFR inhibitors are outside of the NICE scope and were not considered to be appropriate comparators in our submission, the SLR and subsequent ITCs were conducted from a global perspective and as such included a number of comparators not of direct relevance to the UK setting. The full methodology followed in these population-adjusted comparisons alongside the resulting outcomes, were presented in the appendix of our submission.

Given the lack of available evidence to inform a comparison of cemiplimab versus BSC our base case utilised chemotherapy efficacy data as a proxy for BSC (i.e. outcomes for BSC were considered to be no worse than those for chemotherapy – a likely conservative assumption). In order to explore the uncertainty around this assumption pooled data from the EFGR inhibitor studies were used as an alternative proxy for BSC in a scenario analysis. Given the lack of evidence to inform the efficacy of BSC and that there was only limited data on chemotherapy, clinical experts attending an advisory board in the UK indicated that this may be a

reasonable approach given they did not expect EGFRs to be effective in advanced CSCC. Further details on this approach can be found in section B.3.2.3.

A19. Section D.1.3.1: Is the statement that dacomitinib and panitumumab are unlikely to be used to treat advanced CSCC patients based on assumption or evidence? Please provide evidence if possible.

Clinicians consulted in preparation of this evidence submission stated that these unlicensed treatments would not be used in advanced CSCC.

Validation of the dosing regimen

A20. Section B.2.3.1.2 states that "Safety and efficacy data from this 3mg/kg q2w regimen are used to support the proposed dose regimen (350 mg q3w) based on pharmacokinetic (PK) modelling and simulation of exposure, and supported by observed data at 350 mg q3w".

(a) Please provide the results of the PK modelling, and sufficient information on the methods as necessary to enable these results to be interpreted unambiguously.

(b) Please provide the observed exposure data for 350 mg q3w.

Population PK analyses were conducted using the combined cemiplimab concentration datasets from phase I and phase II studies (Groups 1 and 2) to investigate the effect of relevant intrinsic and extrinsic covariates on the PK of cemiplimab. The final population PK model was also used to 1) predict individual post-hoc exposure variables for both phase I and phase II patients to facilitate the exposure-response analyses for efficacy and safety, 2) to simulate exposure after 3 mg/kg Q2W and 350 mg Q3W in patients with any solid tumour and in patients with CSCC, 3) to compare simulated exposure and observed exposure after 350 mg Q3W in patients with CSCC.

Cemiplimab exposure metrics at steady state (Ctrough,ss, Cmax,ss and AUC6wk,ss), shown as median with 95% CI and as mean (CV%), were compared for the 2 dosing regimens (**Table 16** and **Table 17**).

Table 16: Post-Hoc Estimates of Cemiplimab Exposure Parameters at Steady-State Over a 6-Weeks Dosing Period in Patients With Solid Tumours

Metrics	Dose	N	Mean(CV)	SE	SD	Median(CI 95)	GEOmean
[redacted]							

Table 17: Descriptive Statistics of Post-Hoc Analysis for Cemiplimab PK Parameters in Patients with Solid Tumours Estimated at 3 mg/kg Q2W and 350 mg Q3W Regimen Using the Final PK Population Model

3 mg/kg Q2W				350 mg Q3W			
Parameter	Units	Mean(CV)	SD	Parameter	Units	Mean(CV)	SD
[redacted]							

N=505 patients

The parameter AUC6wk,ss was selected to describe exposure over a same observation period, e.g., 3 doses of 3 mg/kg Q2W or 2 doses of 350 mg Q3W. The overall distribution of exposure is shown on the frequency plot (**Figure 5**), with the median AUC6wk,ss for the 350 mg Q3W regimen within 10% of that for weight-based dosing (3 mg/kg Q2W).

Figure 5: Histogram of Post-Hoc Estimates of Steady-State AUC6wk at 2 Dose Regimens of 3 mg/kg Q2W and 350 mg Q3W

Note: The shaded areas represented density of the histogram; the dashed lines represent the medians of the distributions. These data presented are from 2000 simulated patients

Simulation results using the population PK model indicated that: 1) the 350 mg Q3W regimen resulted in similar steady-state exposure compared to the 3 mg/kg Q2W regimen (**Figure 6**), and 2) the variability in cemiplimab exposure (CV% and 90% CI) was similar for the body weight adjusted dose (3 mg/kg Q2W) compared to the 350 mg Q3W dose.

Figure 6: Simulated Concentration-Time Profile (95% Confidence Intervals) of Cemiplimab at 3 mg/kg Q2W or at 350 mg Q3W in Patients with Solid Tumors

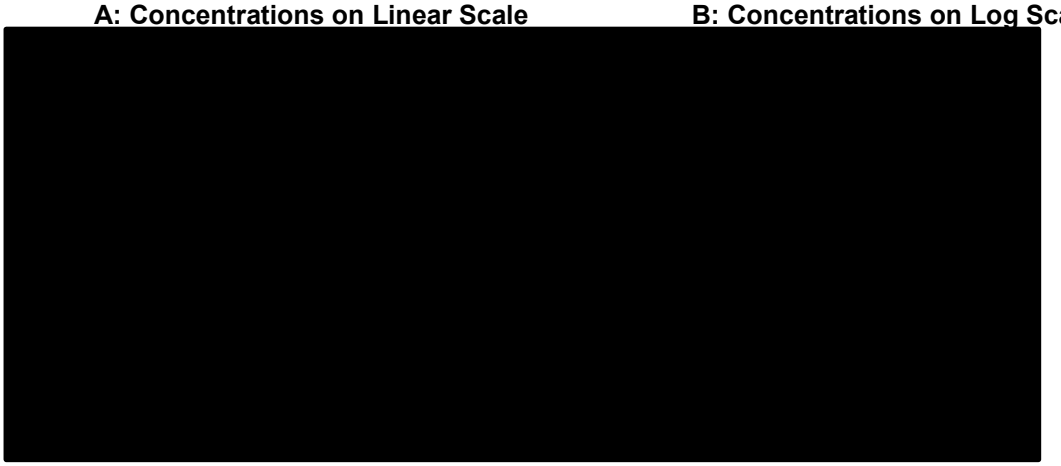
3 mg/kg Q2W **350 mg Q3W**

Note: The black solid line represents the median of 2000 simulated concentration-time profiles, and the gray area shows the 95% CI with 2.5 percentile and 97.5 percentile of the simulated profiles. Note: Each profile is based on 2000 simulated patients

The simulated steady state cemiplimab exposure data for the 350 mg Q3W dose were confirmed by the cemiplimab exposure observed in 16 patients with mCSCC receiving 350 mg Q3W (Group 3) in the phase II study. The observed concentrations in patients who received 350 mg Q3W (35 patients with PK after the first dose, 22 patients with PK during cycle 1, and 16 patients with PK reaching at least 80% of steady state) matched the predicted concentration well, when superimposed on the plot of simulated exposure (**Figure 7**).

Figure 7: 350 mg Q3W Dose Regimen- Observed Cemiplimab Concentrations in Patients with mCSCC and Simulated Cemiplimab Concentration-Time Profiles (95% Confidence Intervals) in Patients With Solid Tumors

A: Concentrations on Linear Scale **B: Concentrations on Log Scale**



The concentration data (C_{eoi} and C_{trough}) from 35 patients with mCSCC who received at least 1 dose of cemiplimab at 350 mg Q3W (Group 3 in phase II study) were overlaid on the simulated concentration-time profiles created using the population PK model.
Note: The black solid line represents the median of 2000 simulated concentration-time profiles, and the gray area shows the 95% CI with 2.5 percentile and 97.5 percentile of the simulated profiles.

The results indicate that the existing population PK model for cemiplimab well describes the observed concentration data for 350 mg Q3W, and further illustrates the similarity of cemiplimab concentrations between the 3 mg/kg Q2W and 350 mg Q3W treatment regimens. By demonstrating similar exposure, these PK analyses facilitate bridging of the datasets, enabling the use of PK, safety and efficacy data from patients receiving 3 mg/kg Q2W, to support the 350 mg Q3W regimen.

Safety

A21. Table 25 in section B.3.3.4: How were these adverse events selected? Please clarify why the percentages in Table 25 differ slightly from those in Table 13 (section B.2.10.2).

In table 13 (section B.2.10.2) of our submission, rates of overall and specific grade 3 or 4 adverse events from the integrated safety analysis of the cemiplimab Phase I and EMPOWER-CSCC 1 trials are presented.

In the economic model, efficacy data for cemiplimab was based on the integrated analysis of the phase I and the phase II, EMPOWER CSCC 1 trials. Efficacy outcomes from the phase II, EMPOWER CSCC 1 trial were reported only for Groups 1 and 2 in which patients received a weight based dose of 3mg/kg. To align with the available efficacy data, adverse events included in the economic model for cemiplimab represented only Groups 1 and 2 of the EMPOWER-CSCC 1 trial and all patients in the Phase I trial. In other words, patients in Group 3 of the EMPOWER-CSCC 1 trial who received the flat dose of 350mg were excluded (Table 25 in section B.3.3.4), which was consistent with the efficacy data used in the economic model.

Other issues related to cemiplimab mode of action

A22. Please confirm whether PD-L1 expression was measured in the patients with CSCC? Does the company plan to measure PD-L1 expression and perform any analyses by PD-L1 expression subgroups?

In our experience, PD-L1 expression levels are not helpful in predicting responses to cemiplimab therapy in advanced CSCC. PD-L1 expression is a dynamic process, and a biopsy obtained from a portion of the tumour in the screening period may not accurately reflect the dynamic immune evasion mechanisms occurring in the cancer.

Biopsies to provide PD-L1 IHC data were not required for advanced CSCC patients in either the phase I or the phase II study, however some biopsies were obtained and these data are being evaluated on an exploratory basis. At the time of the data cut-off, there was insufficient data collected from the phase II study to conduct this analysis. We anticipate that a new data cut will be available for us to share at the time of the technical consultation.

A23. Please confirm whether the development of anti-therapeutic (or "anti-drug") antibodies to cemiplimab was monitored? If so please report the rates and comment on how these compare against other PD-L1 inhibitors.

Among the 534 patients enrolled in the cemiplimab trials, 398 patients had samples analysed for anti-drug antibodies (ADA). The incidence of cemiplimab treatment-

emergent ADAs was [redacted] using an electrochemiluminescent (ECL) bridging immunoassay; [redacted] were persistent ADA responses. In the patients who developed anti-cemiplimab antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab.

A comparison of the rates of anti-therapeutic antibodies to cemiplimab and other PD-1/PD-L1 inhibitors is shown in the table below. This table demonstrates that cemiplimab has the lowest reported rate of anti-therapeutic antibodies of any in the class. However, this comparison has limitations, as the detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab with the incidence of antibodies in other studies or to other products may be misleading.

Table 18: A comparison of the rates of anti-therapeutic antibodies between PD-1 inhibitors

Therapeutic Agent	% Anti-therapeutic antibodies	% neutralizing antibodies	Source of information
Cemiplimab	[redacted]		[redacted]
Pembrolizumab	1.8% (36/2034)	0.4% (9/2034)	SmPC 10/10/2018
Nivolumab	11.4% (231/2022)	0.7% (15/2022)	SmPC 4/10/2018
Atezolizumab	43.9% (192/438)		SmPC 03/09/2018
Avalumab	5.9% (96/1627)		SmPC 13/09/2018
Durvalumab	2.9% (45/1570)	0.5% (8/1570)	SmPC 30/10/2018

Section B: Clarification on cost-effectiveness data

B1. Priority question. The ERG has been unable to replicate cost-effectiveness results presented by the company for the scenarios listed below. Please comment on the following discrepancies in the CE results:

Scenario	Company's results		ERG results	
	ICER vs CT	ICER vs BSC	ICER vs CT	ICER vs BSC

Comparative efficacy: STC	**£38,238**	**£39,952**	**£36,875**	**£38,490**
Treatment benefit cap at 5 years	**£37,726**	**£39,688**	**£39,247**	**£41,346**

We believe that the identified discrepancies stem from the parameterisation of the cost-effectiveness model (CEM) which requires certain steps to be implemented in each case for the results to be replicated.

For the alternative comparative efficacy scenario, based on the STC, the following steps were taken when parametrising the model:

1. The appropriate comparator is set to either chemotherapy or best supportive care (BSC) in cell C58 in the *'Model Parameters'* tab of the CEM.

2. In cell C47 in the *'Apply outcomes from the simulated treatment comparison'* option from the drop down menu the option is switched to *'Yes'.*

3. Then the best fitting parametric distributions that also declined over time are chosen in order to extrapolate the predicted data. In this case, these distributions were Weibull for PFS and Gompertz for OS as discussed in section B.3.3.2.4. These parametric distributions are defined in cells C48 and C49 in the *'Model Parameters'* tab of the CEM for PFS and OS respectively.

For the alternative treatment benefit cap at 5 years, the following steps were taken when parametrising the model:

1. The appropriate comparator is set to either chemotherapy or best supportive care (BSC) in cell C58 in the *'Model Parameters'* tab of the CEM.

2. In cell C50 in the *'Extrapolation of hazard for PFS and OS beyond available data*'* option from the drop down menu the option must be switched to *'Hazard to be equal to chemotherapy (cisplatin)'.* Please note: In this scenario a waning treatment effect is not applied but rather the cemiplimab hazard rate is set to be equal to the chemotherapy hazard rate at the pre-defined time point.

3. Then the time point for extrapolation must be set at 60 months in cell C52. This means that for up to 60 months the cemiplimab treatment effect based on the naïve comparison will continue to apply. Following this, cell C53 must also be set to 60 months in order to prevent the waning treatment effect also being applied in the model. This ensures that after 60 months the hazard rate of cemiplimab is equal to the chemotherapy hazard rate.

B2. Priority question. The ERG was unable to run the following cost-effectiveness scenarios. Please explain how you conducted these analyses in the submitted model:

(a) Using a maximum of 3 treatment cycles for chemotherapy treatment.

In order to set the maximum treatment cycles for the chemotherapy to 3 cycles, a change was made to define the last cycle (in months) of the chemotherapy treatment during the pre-progression state in cells R49 and R53 in the *'Input Drug Costs'* of the CEM. The last cycle in both cells was changed from the base case value of *'4.2'* months which equates to 6 cycles of treatment with chemotherapy (where each treatment cycle equals to 3 weeks) to *'2'* which is a conservative approximation of 3 chemotherapy treatment cycles expressed in months (3 treatment cycles x 3 weeks per cycle = 9 weeks, which is then divided by 4.35 weeks per month to derive the time in months for 3 chemotherapy treatment cycles which is equal to 2.07).

(b) "Long-term extrapolation of cemiplimab, chemotherapy and BSC based on the cemiplimab phase II trial + experts' elicitation and Jarkowski et al 2016 + experts elicitation" (as written in Table 49 in section B.3.8.3)

This analysis was conducted by taking the following steps in the submitted model:

1. The comparator is set to chemotherapy in cell C58 in the *'Model Parameters'* tab of the CEM.

2. In cell C43 in the *'Source of efficacy data'* option from the drop down menu the option is switched to *'Phase II data'.* This analysis was conducted using the phase II trial only since as further explained in section B.3.3.2.3. the expert elicitation exercise was based on data from the phase II trial. Additional details of the design and methodology followed for the experts' elicitation exercise can be found in appendix M.

3. For cemiplimab, the best fitting parametric distributions based on DIC are chosen in order to extrapolate the combined trial data with the experts' estimates. In this case, these distributions were second-order fractional polynomial (p0 p-1) for PFS and Gompertz for OS as discussed in section M.2.3.3. of the appendix. These parametric distributions are defined in cells C48 and C49 in the *'Model Parameters'* tab of the CEM for PFS and OS respectively.

4. Following this, in cell C50 in the *'Extrapolation of hazard for PFS and OS beyond available data*'* option from the drop down menu the option is switched to *'Continuation of hazard trend, using expert information'.*

5. Similarly, for chemotherapy, the best fitting parametric distributions based on DIC were chosen in order to extrapolate the combined trial data with the experts' estimates. In this case, these distributions were Gompertz for PFS and Lognormal for OS as discussed in section M.2.2.2. of the appendix. These parametric distributions are defined in cells C61 and C62 in the *'Model Parameters'* tab of the CEM for PFS and OS respectively.

6. Following this, in cell C63 in the *'Extrapolation of hazard for PFS and OS beyond available data'* option from the drop down menu the option is switched to *'Continuation of hazard trend, using expert information'.*

7. After this parameterisation the resulting ICER is £30,112 versus chemotherapy.

8. In order to generate the same scenario analysis against BSC the following additional steps were taken on top of the above process:

    a. The treatment and administration costs associated with chemotherapy were set to zero in cells O52 and O56 of the *'Input Drug Costs'* tab.

    b. The adverse event rates associated with chemotherapy were set to zero in cells C65 – C70 of the '*Input Safety Tx*' tab.

After this parameterisation the resulting ICER is £31,389 versus BSC.

B3. **Priority question. The adverse event rates for cemiplimab in the model (CS Table 25 in section B.3.3.4) are not consistent with the modelled treatment, as patients receiving a flat dose were excluded. The included types of adverse event and event rates are also inconsistent with results reported for the safety analysis set in CS section B.2.10.2 Table 12 and 13.**

Please explain how you derived the lists of included events and the event rates in Tables 25 and 26.

Please also provide a complete list of adverse events from the integrated analysis safety population (n=163) comparable to Table 3 for the Platinum-Fluorouracil arm of the Vermorken et al study (NEJM 2008). This should include all grade 3-5 events with an incidence of 1% or higher in either study.

In the economic model, rates of grade 3 and 4 adverse events for cemiplimab were based on data from the Phase 1 (n=26) and EMPOWER CSCC 1 (n=114) trials. As noted in the response to question A21, adverse event rates for cemiplimab excluded Group 3 of the EMPOWER CSCC 1 trial to remain consistent with the population used to derive the efficacy outcomes. **Table 19** shows the full list of adverse events included in the model, which were selected based a threshold of ≥5% in any study.

Where more than one trial reported adverse events for an intervention or comparator, the adverse event rates were pooled using inverse weighted variance. Please see **Table 20** for rates for each intervention following pooling using inverse weighted variance.

Please see **Table 21** for grade 3 or 4 adverse events occurring in ≥1% of patients in the cemiplimab integrated analysis (Table 13 of our submission) and the Vermorken et al (2013) study.[1-3] The Vermorken et al (2013) study was identified through a targeted literature review of studies for patients with advanced cancer treated with cisplatin and 5-FU. It was considered the most relevant study given that, as suggested by clinical experts, squamous cell carcinoma of head and neck (HNSCC) would be the closest tumour type to borrow data from given the absence of specific advanced CSCC data. A comparison of the baseline characteristics between the control arm of the Vermorken et al (2013) trial and the integrated cemiplimab efficacy analysis suggested the trials were generally comparable; the proportion of males enrolled in the trials was similar (87% and [redacted], respectively). However, the Vermorken et al (2013) trial included younger patients (average age of 59 years old versus [redacted] years old) and the ECOG was generally poorer (69% of patients with ECOG of 1 versus [redacted]). Whilst such differences are expected between the advanced CSCC and HNSCC populations, Vermorken et al (2013) was considered to be the best available source for AEs specific to the administration of platinum-based chemotherapy.

Of note, the results of the base case analysis versus chemotherapy found the total cost of adverse events to be [redacted] and [redacted] for cemiplimab and chemotherapy, respectively. The total adverse event disutility was estimated as [redacted] for cemiplimab and [redacted] for chemotherapy. The difference accounts of [redacted] of the total incremental cost and [redacted]

of the total incremental QALY gain, highlighting that the impact of using alternative assumptions, regarding adverse events, is likely to be minimal on the overall cost-effectiveness.

Table 19: Adverse events reported in trial data for intervention and comparators

Adverse event	Cemiplimab		Chemotherapy
	Phase 1[1]	EMPOWER CSCC 1[2]	Vermorken et al (2013)[3]
Skin infection	[redacted]	[redacted]	NR
Hypercalcaemia	[redacted]	[redacted]	NR
Failure to thrive	[redacted]	[redacted]	NR
Fatigue	[redacted]	[redacted]	NR
Infection	[redacted]	[redacted]	NR
Infusion related reactions	[redacted]	[redacted]	*0%*
Rash, acne	[redacted]	[redacted]	NR
Tumour bleeding	[redacted]	[redacted]	NR
Hypokalaemia	[redacted]	[redacted]	**7.1%**
Stomatitis or oral mucositis	[redacted]	[redacted]	**8.6%**
Neutropenia	[redacted]	[redacted]	**32.6%**
Anaemia	[redacted]	[redacted]	**14.5%**
Thrombocytopenia	[redacted]	[redacted]	**7.7%**
Febrile neutropenia	[redacted]	[redacted]	**5.2%**

Notes: *Adverse events highlighted in bold represent those reported in ≥5% of patients, those italicized represent adverse events included in the economic model for consistence with other trials where adverse events are reported in ≥5%.*

Table 20: Adverse event rates following inverse proportional weighting

Adverse event	Cemiplimab[1,2]	Chemotherapy (cisplatin +5-FU)
Skin infection	[redacted]	0.0%
Hypercalcaemia	[redacted]	0.0%
Failure to thrive	[redacted]	0.0%
Fatigue	[redacted]	0.0%
Infection	[redacted]	0.0%
Infusion related reactions	[redacted]	0.0%
Rash, acne	[redacted]	0.0%
Tumour bleeding	[redacted]	0.0%
Hypokalaemia	[redacted]	7.1%
Stomatitis or oral mucositis	[redacted]	8.6%
Neutropenia	[redacted]	32.6%

Adverse event	Cemiplimab[1,2]	Chemotherapy (cisplatin +5-FU)
Anaemia	[redacted]	14.6%
Thrombocytopenia	[redacted]	7.7%
Febrile neutropenia	[redacted]	5.2%

Abbreviations: *5-FU, fluorouracil.*

Table 21: Grade 3 or 4 adverse events occurring in >1% of patients in the integrated analysis of cemiplimab trials or Vermorken 2013

Adverse event	Integrated analysis (N=163),[1,2] n (%)	Vermorken et al (2013),[3] control group (n=325), n (%)
Acute kidney injury	[redacted]	NR
Acute renal failure	[redacted]	11 (3.3)
Anaemia	[redacted]	47 (14.4)
Arthralgia	[redacted]	NR
AST increase	[redacted]	NR
Atrial fibrillation	[redacted]	NR
Autoimmune hepatitis	[redacted]	NR
Cardiac arrhythmias	[redacted]	8 (2.4)
Cellulitis	[redacted]	NR
Death	[redacted]	NR
Dehydration	[redacted]	7 (2.1)
Delirium	[redacted]	NR
Diarrhoea	[redacted]	4 (1.2)
Dysphagia	[redacted]	NR
Embolic and thrombotic events[a]	[redacted]	5 (1.5)
Failure to thrive	[redacted]	NR
Fatigue	[redacted]	NR
Febrile neutropenia	[redacted]	17 (5.2)
Hypercalcaemia	[redacted]	NR
Hypertension	[redacted]	NR
Hypocalcaemia	[redacted]	7 (2.1)
Hypokalaemia	[redacted]	23 (7.0)
Hypomagnesaemia	[redacted]	12 (3.6)
Hyponatraemia	[redacted]	NR
Myocardial infarction	[redacted]	NR
Neutropenia	[redacted]	106 (32.6)
Pain in extremity	[redacted]	NR
Pleural effusion	[redacted]	NR
Pneumonia	[redacted]	NR
Pneumonitis	[redacted]	NR
Rash maculo-papular	[redacted]	NR
Sepsis	[redacted]	NR
Skin eyes or both	[redacted]	6 (1.8)
Skin infection	[redacted]	NR

Adverse event	Integrated analysis (N=163),[1,2] n (%)	Vermorken et al (2013),[3] control group (n=325), n (%)
Stomatitis or oral mucositis	[redacted]	28 (8.6)
Syncope	[redacted]	NR
Thrombocytopenia	[redacted]	25 (7.6)
Urinary tract infection	[redacted]	NR
Venous embolic and thrombotic events	[redacted]	6 (1.8)

Notes: a) *Uunspecified or mixed vessel type.* ***Abbreviations:*** *NR, not reported.*

B4. Please explain the rationale for your selection of adverse event utility decrements in Table 27 (section B.3.4.4) and costs in Table 39 (section B.3.5.4). Why did you select different NICE technology appraisals as the sources for different adverse events?

Please also explain why you apply the same assumed duration of 30 days for all adverse events?

A targeted literature review was conducted to identify the most frequently cited sources of adverse event utility decrements included in technology appraisal submissions to NICE. The review included appraisals of technologies for the treatment of a variety of cancers such as melanoma, basal cell carcinoma, merkel cell carcinoma, and squamous cell carcinoma of the head and neck. Appraisals of immunotherapies (nivolumab, pembrolizumab and atezolizumab) were also targeted for review. The most frequently cited studies included Nafees et al (2008), Lloyd et al (2006), and Tolley et al (2013). (see **Table 22**).

A similar approach was adopted for estimating the costs of adverse events (see **Table 23**). Where the unit costs of adverse events could not be identified from prior technology appraisals, costs were estimated from the NHS Reference costs 2016/17. Included costs of adverse events were generally in line with those presented in prior NICE appraisals.

Evidence was not available to inform the duration of each adverse event; therefore, a conservative assumption was made where the duration of all adverse events was assumed to be one cycle (30.4 days).

Table 22: Adverse event utility decrements included in the economic model

Adverse event	Mean	SE	Source	Rationale
Skin infection	0.120	0.005	Cellulitis, Amgen (2014) utility study for advanced melanoma	Assumed to be the same as cellulitis, in NICE TA410.
Hypercalcaemia	0.090	0.015	Neutropenia, Nafees (2008)	Assumed to be the same as hyponatremia in NICE TA517.
Failure to thrive	0.073	0.018	Fatigue, Nafees (2008)	Assumed to be same as fatigue.
Fatigue	0.073	0.018	Fatigue, Nafees (2008)	Assumed to be same as fatigue, in NICE TA490.
Hypokalaemia	0.090	0.015	Neutropenia, Nafees (2008)	Assumed to be the same as hypercalcaemia.
Stomatitis or oral mucositis	0.151	0.036	Stomatitis, Lloyd (2006)	AE event and AE utility decrement are aligned.
Neutropenia	0.090	0.015	Neutropenia, Nafees (2008)	AE event and AE utility decrement are aligned.
Anaemia	0.073	0.018	Fatigue, Nafees (2008)	Assumed to be the same as anaemia in NICE TA517.
Thrombocytopenia	0.108	0.010	Thrombocytopenia, Tolley (2013)	AE event and AE utility decrement are aligned.
Febrile neutropenia	0.090	0.016	Febrile Neutropenia, Nafees (2008)	AE event and AE utility decrement are aligned.

Abbreviations: *NICE, National Institute of Health and Care Excellence; TA, Technology Appraisal; SE, standard error.*

Table 23: Adverse event utility decrements included in the economic model

Adverse event	Unit Cost	Reference	Rationale
Skin infection	£143.20	Cost assumed to be the same as for cellulitis in NICE TA410, has been inflated using the PSSRU 2017 HCHS index.	Assumed to be same as cellulitis, NICE TA410.
Hypercalcaemia	£1,139.92	NHS reference costs 2016/17: KC05G,H,J,K,L,M,N Fluid or Electrolyte Disorders.	Similar cost estimation approach as adopted for hypophosphataemia in TA519.
Failure to thrive	£3,179.70	Assumed to be same cost as fatigue	Assumed to be same as Fatigue, TA490.
Fatigue	£3,179.70	Cost assumed to be the same cost of fatigue as in NICE TA490, has been inflated using the PSSRU 2017 HCHS index.	Assumed to be same as Fatigue, TA490.
Hypokalaemia	£1,139.92	NHS reference costs 2016/17: KC05G, H, J, K, L, M, N Fluid or Electrolyte Disorders. Weighted cost of non-elective long stay, short stay and day case.	Similar cost estimation approach as adopted for hypophosphatemia in TA519.
Stomatitis or oral mucositis	£998.38	Assumed to be same cost as Nausea and Vomiting in Brown 2013, where a typical patient will	Assumption.

Adverse event	Unit Cost	Reference	Rationale
		have two admissions during chemotherapy, each costing £443.54. Inflated to 2016/17 prices using the PSSRU HCHS inflation indices 2017.	
Neutropenia	£325.49	NHS reference costs 2016/17: WJ11Z, Other Disorders of Immunity.	Similar cost estimation approach adopted in TA519, assuming all patients require hospitalization.
Anaemia	£1,273.72	NHS reference costs 2016/17: SA01K, J, H, G Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia. Weighted cost of non-elective long stay, short stay and day case.	Cost estimation approach adopted in TA490.
Thrombocytopenia	£325.49	NHS reference costs 2016/17: WJ11Z, Other Disorders of Immunity.	Assumed same as neutropenia.
Febrile neutropenia	£2,688.94	The NICE DSU report on the cost of febrile neutropenia 2007 (£2,286) has been inflated to 2016/17 prices using the PSSRU HCHS index 2017.	Cost estimation approach adopted in TA519.

Abbreviations: *PSSRU, Personal and Social Services Research Unit; NHS, National Health Service; NICE, National Institute of Health and Care Excellence.*

B5. PFS and OS estimates from expert elicitation are presented for chemotherapy in Figures 31 and 32 (section B.3.3.2.5). However, for cemiplimab, estimates from expert elicitation are only presented for OS (Figure 26) but not for PFS (section B.3.3.2.3). Please explain whether there is a reason for this difference between the modelled treatments?

Apologies, this was an oversight during the preparation of the evidence submission for cemiplimab.

The relevant figure depicting the long-term progression-free survival estimates from the extrapolated curves when compared with experts' long-term progression-free survival estimates based on the Phase II trial data can be found in **Figure 8** below. As can be seen in **Figure 8**, in line with the OS extrapolation results, the long term PFS estimates derived from the extrapolations in the base case are also more conservative than those based on the experts' elicitation. A scenario analysis utilising the results for both chemotherapy and cemiplimab from the expert elicitation exercise

was provided in section B.3.8.3. Additional details around the experts' elicitation exercise can be found in appendix M.

Figure 8: Expected outcomes of PFS based on best fitting model with and without expert information for cemiplimab from the Phase II, EMPOWER-CSCC 1 trial

Section C: Textual clarifications and additional points

C1. Please provide footnotes a and b for Figure 4 in section B.2.1.

Footnote a: citations that also included patients with resectable laCSCC (n=4), citations that also included patients with local CSCC (n=6).

Footnote b: inclusion of two narrative reviews, a citation in German and a conference abstract corresponding to a full-text citation (Nottage 2017) with no additional data.

C2. Please provide footnote a for Table 7 in Appendix D.

Footnote a: only efficacy outcomes were used for study selection, although, all outcomes listed were extracted.

C3. Please provide footnote c for Table 8 in Appendix D.

Footnote c: as opposed to ear or lip.

C4. In Table 18 in section B.3.3.1 the sample sizes reported in the "Source/justification" column are the same for males and females. Please confirm whether these are typos?

The sample sizes reported in the "Source/justification" column refer to the total patient numbers from each of the trial.
Male patient characteristics are based on 21 patients from the Phase I study and 71 patients from the phase II, EMPOWER-CSCC 1 study.
Female patient characteristics are based on 5 patients from the Phase I study and 11 patients from the phase II, EMPOWER-CSCC 1 study.

C5. The title to Figure 31 in section B.3.3.2.5 states that observed PFS data was combined with OS from the expert elicitations. Please confirm whether this is a typo?

This was an oversight in our submission and it should read 'combined with PFS'.

References

1. Sanofi. A First-in-Human Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death – 1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies, in Patients with Advanced Malignancies. (Clinical Study Report) 22 February 2018 2018. Data on File.
2. Sanofi. A Phase 2 study of REGN2810, a fully human monoclonal antibody to programmed death-1 (PD-1) in patients with advanced cutaneous squamous cell carcinoma. (Clinical Study Report) 2018. Data on File.
3. Vermorken JB, Stohlmacher-Williams J, Davidenko I, et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. *Lancet Oncol.* 2013;14(8):697-710.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

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.

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- 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	**Consultant Dermatologist**
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 charity 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.
5b. 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.)	
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.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the	

condition, and if so, which?	
• 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.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be	

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
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?	
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?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
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?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

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

- The plastic surgeons society (BAAPS) should be included in the consultation
-
-
-
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP**

3. Job title or position	**RCP registrar**
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).	**NCRI-ACP-RCP**
5b. 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,	To stop progression and prolong life.

or prevent progression or disability.)	
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.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a huge unmet clinical need for patients with metastatic cutaneous squamous cell carcinoma (cSCC). There are no reliable treatments once this cancer has spread and conventional chemotherapy and EGFR inhibitors have <25% survival at 5 years. Furthermore, many high-risk patients present with multiple primary malignancies leading to considerable surgical complexity and morbidity. The incidence of cSCC is increasing steeply in our ageing population in large part because of relative immunosuppression due to cumulative UV exposure and old age. An immunotherapy is a logical treatment for use in this devastating disease, especially as molecular profiling of cSCC finds it to be a highly mutated cancer with potentially suitable tumour antigens.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Surgery is the mainstay of therapy for cSCC. Local recurrence and loco-regional spread will usually be treated with surgery plus/minus adjuvant radiotherapy. If surgery is unsuccessful or inappropriate, patients will be treated with radiotherapy. If cSCC recurs within a previous radiotherapy field or if there is distant metastasis, there are no reliable treatments. Standard chemotherapy (Cisplatin +/- 5-FU) and EGFR inhibitors (e.g. cetuximab) will occasionally show useful responses, but data supporting efficacy is limited.

	Palliative care is the most frequent 'non-treatment choice' for an elderly patient with metastatic cutaneous squamous cell carcinoma.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are dermatology guidelines available which cover primary cSCC, but these do not cover management of metastatic cSCC and typically just advise that this is managed through the local/regional multi-disciplinary team and/or referred for clinical trials. The most recent UK Dermatology Guidelines are the British Association of Dermatology 2009 and the Scottish Intercollegiate Guidelines Network (SIGN) 2014. The BAD Guidelines Development group are currently in session to update the guidelines for management of cutaneous SCC. Internationally, the NCCN Guidelines (2012) recommend clinical trials for metastatic cSCC, recognising that there is no accepted treatment currently.
• 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.)	No, the pathway of care is not well defined. It will vary according to local resources and local opinions on the skin cancer MDTs.
• What impact would the technology have on the current pathway of care?	It would become an invaluable additional tool to use in this devastating condition that currently has no effective treatments once metastatic.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, similar class of immunotherapy (e.g. pembrolizumab and nivolumab) are already in use in the NHS for patients with melanoma. These are also PD-1/PD-L1 inhibitors and I anticipate that cemiplimab would be used identically.

• How does healthcare resource use differ between the technology and current care?	It would be very similar to pembrolizumab which is already established in current care for melanoma.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, oncology clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It would be important to combine introduction of cemiplimab with translational research to investigate which biomarkers (e.g. PD-L1 immunohistochemistry – already available for routine NHS testing for melanoma) are the best indicators of response. Similarly, it would be important to document side effects and outcomes and examine whether more efficacy and more sustained responses are seen in patients in whom radiotherapy is use first or concurrently (theory may expose tumour antigens increasing efficacy of immune checkpoint inhibitor).
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• 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, although this treatment like other immune checkpoint inhibitors has quite a significant toxicity profile. However, we are becoming much more expert at dealing with these toxicities so overall if the treatment works, our experts note that a significant increase in health-related quality of life should be expected.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Many patients with metastatic cSCC are immunosuppressed solid organ transplant recipients (SOTR). There is a likelihood that use of Cemiplimab in these patients will lead to rejection of their allograft. Although this is less of a problem for kidney or kidney/pancreas transplants (the patient can return to dialysis), it is a significant risk to life for liver transplants, heart transplants and lung transplants. Therefore, apart from renal transplantation, our experts expect it to be too high risk for other SOTR.
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	As discussed above, Cemiplimab is an immune checkpoint inhibitor (ICi) and like other ICi already in use (pembrolizumab, novolumab), one would expect potentially serious immunologically-based adverse effects (in about 15%, leading to drug withdrawal in about 7%)s. However, we are becoming much more expert at dealing with these toxicities so this should be no different than for ICi currently in standard clinical practice. It would probably be important to measure PD-1/PD-L1 immunohistochemistry on tumour (as part of pathology work up) to see whether this correlates with response.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, our experts think that this would be unwise as we do not know how best to predict response and at this stage we should be documenting outcome and biomarkers and adjuvant therapies and building up an evidence base for best practice.
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?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, it will be the first treatment to offer potentially long-term survival benefits in a majority of patients. Although efficacy with EGFR inhibitors is reported, the number responding is low (<10%) and it is not clear which patients will respond.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
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?	As above (see 13), our experts expect potentially severe immunologically-based adverse events in up to 15%. These can usually be treated satisfactorily with drug withdrawal and short-term, high dose corticosteroids. This will impact the patient's QoL, but the alternative is death so the patient is usually willing to take this risk.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	No, this class of immunotherapy is not current UK clinical practice for cSCC, although it is in regular use for melanoma. There has been a phase 1 clinical trial of Cemiplimab with two Phase 2 expansion cohorts showing 47-50% response in patients with metastatic cSCC (Migden MR, et al. NEJM June 4, 2018).
• If not, how could the results be extrapolated to the UK setting?	Ideally, PD-1 and PD-L1 inhibitors would become standard care in the UK, when clinically indicated.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free survival, overall survival, duration of response and toxic effects.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable, no need to use surrogates
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might	Our experts note anecdotal case reports for use of this class of drug in patients with solid organ transplants and their outcomes.

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No comparator. The only clinical trial data was a non-randomised study without a comparator as there is no alternative treatment for this condition currently.
21. How do data on real-world experience compare with the trial data?	No real-world experience data
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	Not applicable

Key messages

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

- Huge unmet clinical need for an effective treatment for metastatic cutaneous SCC (none currently)
- Good theoretical rationale for why this treatment should be effective in cutaneous SCC
- Clinical trial data (admittedly limited and non-randomised) found 50% response rate which is significantly superior to either standard chemotherapy (Cisplatin +/- 5-Fluorouracil) or EGFR inhibitors (e.g. cetuximab)
- This class of anti-PD-1 monoclonal antibody is already in regular clinical use for melanoma so there is considerable experience amongst oncologists in how to monitor and manage the side effects
- Immune-related side effects are expected and may be severe in approx. 15% cases, leading to withdrawal of treatment in approx. 7%

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Charlotte Mary Proby**
2. Name of organisation	**University of Dundee and NHS Tayside**

3. Job title or position	**Professor of Dermatology**
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):
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)	☒ 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. 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	
7. 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 aim of any PD1 inhibitor immunotherapy is to stop disease progression and give a durable remission from the squamous cell cancer. This is through activation of the host immune response against the cancer.
8. 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 clinically significant treatment response would be reduction in tumour size or in metastatic lymph nodes of any amount provided it was durable. An excellent treatment response would be disease remission.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a huge unmet need. There is no effective chemotherapy or targeted treatments for metastatic cutaneous SCC. Sometimes radiotherapy can be helpful, but usually the disease will escape. EGFR inhibitors are used in some cases and whilst there is often an initial response this is seldom sustained. Overall, EGFR inhibitors have a modest effect as monotherapy or in combination (Overall Response Rate 7-28%; median Progression Free Survival only 3.8-4.7 months). EGFRi are also pretty toxic and poorly tolerated by elderly patients. Metastatic cutaneous SCC is usually found in elderly patients, often very elderly and frail patients. There is a real paucity of treatments for this devastating disease.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	It depends on the age and frailty of the patient. Many patients with metastatic cSCC are elderly and/or frail. In these cases, they may be offered radiotherapy or may go straight to palliative care. Cutaneous SCC and metastatic cutaneous SCC are both significantly more common in patients who are immunosuppressed e.g. because of a solid organ transplant. In a renal transplant recipient where there is an option to go back on dialysis, a common treatment would be to stop immunosuppression and hope the SCC stabilises.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Very few of the clinical guidelines currently in use give advice about treatments for metastatic cutaneous SCC. The UK guidelines for cutaneous SCC are being updated by the British Association of Dermatologists and I am on the guideline development board. They will contain a short piece about available treatments for metastatic cSCC, but there is no evidence to support any specific treatment currently available so the recommendation will be weak.
• 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.)	The pathway of care is not well defined because metastatic cSCC is relatively rare and because there have been no controlled trials and data are weak and inconsistent. Consequently, it does vary across the NHS, but most clinicians looking after patients with metastatic cSCC will try chemotherapy or radiotherapy or just refer for palliative care. The most commonly used chemotherapy regimens are 5-fluorouracil/cisplatin or 5-FU/carboplatin, or paclitaxel/carboplatin combinations. Sustained remissions are rare and traditional chemotherapy is poorly tolerated by elderly frail patients who make up the majority of those with advanced cSCC. My clinical experience is purely within the NHS. I currently work in Scotland. I am the UK-representative on the International Transplant Skin Cancer Collaboration and from this I am aware of other management pathways, for instance in the US and in Australia. In the US, anti-PD1 agents are already being used.
• What impact would the technology have on the current pathway of care?	This technology would have significant impact and is likely to become the treatment of choice in metastatic cSCC unless the patient is an organ transplant recipient in which case the technology will not be appropriate as it is very likely to induce allograft rejection.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology is already in use for treatment of metastatic melanoma and other malignancies such as Merkel cell carcinoma, lung cancer or renal carcinoma. I would envisage that it would be used in a similar way for metastatic cutaneous SCC.
• How does healthcare resource use differ between the technology and current care?	This immunotherapy is not currently licensed for use in advanced cutaneous SCC
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care by oncologists
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Not much investment would be needed since this class of drug is already in use for metastatic melanoma so oncologists looking after patients with skin cancer will be familiar with how to use anti-PD1 therapy, what toxicities to look out for and how to manage these toxicities.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, undoubtedly

• Do you expect the technology to increase length of life more than current care?	Yes, in a meaningful proportion of patients I would expect to see increased progression free survival and increased overall survival compared with current care, although the inability to use this treatment for organ transplant recipients (it will induce rejection of their allograft) is a problem.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, I would expect to see increased health-related quality of life, although the drug toxicities are not insignificant and need to be taken account of when treating the elderly and frail.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, I would expect to see less efficacy in anyone with a compromised immune system and it would be contraindicated in organ transplant recipients as discussed above. The majority of patients are likely to be elderly and in this group of patients it is unclear how well this treatment would work as they will have a relatively less efficient immune system.
The use of the technology	
14. 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	The side effect profile is very different from traditional chemotherapy or radiotherapy. Patients develop 'autoimmune' toxicities, but this class of drug is already in widespread use for other cancers and oncologists are becoming more adept at treating the toxicities effectively so I don't see any particular difficulties in introducing this technology for cutaneous SCC. The potential endocrine toxicities (e.g. hypopituitary, hypoadrenal or hypothyroid may need to be tested for.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	See above concerning toxicities. Many of these can be managed with corticosteroids, but if severe the treatment may need to be stopped. It usually takes several months to see benefit with immune checkpoint inhibitors because it takes this long to efficiently boost the anti-cancer immune response. If no benefit has been seen after 6 months of use, I would expect the treatment to be stopped.
16. 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?	No. I would expect QALY calculations to be appropriate as I would expect to see significant prolongation of life and increased progression free survival.

17. 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 indeed. There is a real paucity of effective treatments currently so this technology would make a huge difference.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As discussed above, this group of drugs have a very particular immune-related side effect profile but management of such toxicities is usually possible and oncologists are becoming increasingly experienced in doing so.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Not yet for cutaneous SCC, although yes for other skin cancers such as melanoma where use of immune checkpoint inhibitors (and specifically anti-PD1 drugs) is now mainstream clinical practice.
• If not, how could the results be extrapolated to the UK setting?	The results can be extrapolated to the UK setting
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are progression free survival and overall survival and these were measured in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcome measures were not used
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is some anecdotal evidence of use of this technology in organ transplant recipients (they were excluded from the trials). In most cases the allograft was rejected. In a minority of cases the allograft survived.
21. How do data on real-world experience compare with the trial data?	I don't know, but I would expect it to compare similarly if real-world experience with metastatic melanoma is anything to go by.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	Not appropriate
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- There is a very significant unmet clinical need for this devastating disease
- It is likely that a significant proportion of patients (perhaps 50%) will be given disease control or remission by introduction of this technology. This will be life prolonging.
- The side effect profile of this treatment is well understood and usually can be managed with corticosteroids
- This treatment is not suitable for organ transplant recipients which is an important deficiency since these patients are more likely to get this disease
- This treatment may not be so effective or so suitable for the elderly frail patient and again these patients are more likely to get this disease

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

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.

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- 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	**The Christie Hospital NHS Foundation Trust**

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. 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	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow the progression of disease.
8. 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 objective response rate greater than currently available chemotherapy options. These provide at best a 20% objective response rate.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Currently patients who are fit enough are treated with palliative chemotherapy. There is no established regime, but in most cases a platinum/5FU regime is used along the lines of similar head and neck SCC chemotherapy regimens. Many patients however are elderly and do not tolerate platinum chemotherapy, so this option is not available to them. Currently they have no viable treatment option.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no established guidelines. The management of metastatic/inoperable cSCC has suffered from a lack of research and investment, and there are no well documented, effective chemotherapy regimens. Treatment tends to be based on chemotherapy regimens use in head and neck SCC, though cSCC does not respond as well. In practice it is rare to see patients respond to chemotherapy.
• 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.)	The pathway of care is not well defined once patients are diagnosed with inoperable/metastatic cSCC. Within the NHS care will vary depending on the opinion and expertise of the treating physician.
• What impact would the technology have on the current pathway of care?	It would provide an evidence based treatment pathway for patients with inoperable/metastatic cSCC. Cemiplimab would replace the variety of ad hoc, largely platinum based, chemotherapy regimens with little or no evidence base for their use.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In the tertiary setting. Treatment should only be prescribed by specialist trained in the use of chemotherapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment is needed. Oncologists are already familiar with the use of immunotherapy and the facilities required are already in place and used to provide chemotherapy.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Phase II studies show a 47% response rate for patients with metastatic/inoperable cSCC.
• Do you expect the technology to increase length of life more than current care?	While the relevant clinical trial is phase II and so has no direct comparison against best current care, the response rate of 47%, and 61% survival beyond 6 months is strongly suggestive that this drug will prolong life.
• Do you expect the	Yes, again while the relevant evidence is phase II with no direct comparison, similar immunotherapy trials

technology to increase health-related quality of life more than current care?	with lower response rates have shown significant improvements in quality of life. Certainly compared to chemotherapy, cemiplimab has a significantly better toxicity profile.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology would not be expected to be effective, or appropriate, in patients who are immune-compromised, or who have auto-immune diseases.
The use of the technology	
14. 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	This technology will be easier to administer than conventional chemotherapy because of its lower toxicity. Numerous studies of immunotherapy have shown that it is more acceptable to patients than chemotherapy.

<table>
<tr><td>or ease of use or additional tests or monitoring needed.)</td><td></td></tr>
<tr><td>15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?</td><td>
The following are the eligibility criteria for inclusion in the SANOFI compassionate use program. I would anticipate similar criteria for clinical use.
Treatment will be stopped on evidence of progression.

<table>
<tr><td>≥18 years old</td><td>☐</td><td>☐</td></tr>
<tr><td>Hepatic function:
• Total bilirubin ≤1.5 x upper limit of normal (ULN; if liver metastases ≤3 x ULN). Patients with Gilbert's Disease and total bilirubin up to 3 x ULN are eligible.
• Transaminases ≤3 x ULN (or ≤5.0 x ULN, if liver metastases)
• Alkaline phosphatase (ALP) ≤2.5 x ULN (or ≤5.0 x ULN, if liver or bone metastases)
*Patients with hepatic metastases: If transaminase levels (AST and/or ALT) are >3 x but ≤5 x ULN, total bilirubin must be ≤1.5 x ULN. If total bilirubin is >1.5 x but ≤3 x ULN, both transaminases (AST and ALT) must be ≤3 x ULN.</td><td>☐</td><td>☐</td></tr>
<tr><td>Renal function:
Serum creatinine ≤1.5 x ULN or estimated creatinine clearance (CrCl) >30 mL/min</td><td>☐</td><td>☐</td></tr>
<tr><td>Bone marrow function:
a. Haemoglobin ≥9.0 g/dL
b. Absolute neutrophil count (ANC) ≥1.5 x 109/L
c. Platelet count ≥75 x 109/L</td><td>☐</td><td>☐</td></tr>
</table>
<table>
<tr><th>ELIGIBILITY CRITERIA
(A patient who meets any of the following criteria cannot be included into the Named Patient Supply)</th><th colspan="2">Mark or check correct answer</th></tr>
<tr><th></th><th>Yes</th><th>No</th></tr>
<tr><td>Patients with a history of solid organ transplant (patients with prior corneal transplant(s) may be allowed to enroll after discussion with and approval from the sanofi medical review committee).</td><td>☐</td><td>☐</td></tr>
<tr><td>Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required</td><td>☐</td><td>☐</td></tr>
</table>
</td></tr>
</table>

	treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.			
	Prior treatment with an agent that blocks the PD-1/PD-L1 pathway	☐	☐	
	Prior treatment with other immune modulating agents that was (a) within fewer than 4 weeks (28 days) prior to the first dose of cemiplimab (REGN2810), or (b) associated with immunemediated adverse events that were ≥ grade 1 within 90 days prior to the first dose of cemiplimab , or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent. (Examples of immune modulating agents include therapeutic anti-cancer vaccines, cytokine treatments (other than G-CSF or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), or OX-40)	☐	☐	
	Untreated brain metastasis(es) that may be considered active (Note: patients with brain involvement of CSCC due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily). Patients with previously treated brain metastases may participate provided that the lesion(s) is (are) stable (without evidence of progression for at least 4 weeks on imaging), and there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 2 weeks of first dose of cemiplimab)	☐	☐	
	Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab. Note: Patients who require brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded.	☐	☐	
	Active infection requiring therapy, including infection with human immunodeficiency virus, or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).	☐	☐	
	History of non-infectious pneumonitis within the last 5 years	☐	☐	

	Grade ≥ 3 hypercalcemia at time of enrollment	☐	☐	
	Any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of cemiplimab or planned to occur during treatment with cemiplimab (Patients receiving bisphosphonates or denosumab are not excluded), radiation therapy within 14 days of initial administration of cemiplimab planned to occur during treatment with cemiplimab	☐	☐	
	History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments.	☐	☐	
	Patients with allergy or hypersensitivity to cemiplimab or to any of the excipients must be excluded. Specifically, because of the presence of trace components in cemiplimab, patients with allergy or hypersensitivity to doxycycline or tetracycline are excluded.	☐	☐	
	Breast feeding	☐	☐	
	Positive serum pregnancy test	☐	☐	
	Continued sexual activity in men or women of childbearing potential who are unwilling to practice highly effective contraception during the Supply and until 6 months after the last dose of cemiplimab. (Highly effective contraceptive measures include stable use of oral contraceptives such as combined estrogen and progestogen and progestogen only hormonal contraception or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to treatment start; intrauterine device [IUD]; intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomy, and sexual abstinence).	☐	☐	
	Concurrent malignancy other than CSCC	☐	☐	
	Any acute or chronic psychiatric problems that, in the opinion of the physician, make the patient ineligible for participation.	☐	☐	
	Prior treatment with idelalisib	☐	☐	
	Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the physician, renders the patient unsuitable for participation in the NPS due to high safety risks.	☐	☐	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are	Not known			

unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. 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. Cemiplimab fills an unmet need in the treatment of metastatic/inoperable cSCC. It offers a treatment, where previously there was no proven effective treatment.
• Is the technology a 'step-change' in the management of the condition?	Yes.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. There is no proven existing treatment for metastatic/inoperable cSCC.
18. How do any side effects or adverse effects of the	The side effect profile is such that cemiplimab is well tolerated. Side effects are fewer than those of

technology affect the management of the condition and the patient's quality of life?	commonly used chemotherapies.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	UK practice is where the patient is fit, is to use platinum based chemotherapy. The current trial was phase II, so the question is not really applicable. It is however in the sense that the treatment of metastatic/inoperable cSCC is an unmet need, so any effective treatment would be welcome in the UK setting.
• 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 improvement in overall survival over platinum chemotherapy. This was not measured in a phase II study. The Objective response rate and overall survival however are impressive in this setting.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Immunotherapy trials often show low response rates, but better overall survival than against comparator chemotherapy. In this context the objective response rate of 47% is very impressive (cf approx. 20% for pembrolizumab in keynote 048 which still showed an improved survival over chemotherapy with a 36% response rate) and would suggest that cemiplimab will provide a significant survival advantage over

	chemotherapy or best supportive care.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Unlikely given the consistent side effects of immunotherapy agents.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	There is insufficient real world experience to compare.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	NA.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Despite the incidence of non-melanoma skin cancer increasing by two thirds in the last decade, it has always been a “hidden” cancer that has attracted only limited support and investment for research and development.
- Metastatic/inoperable cutaneous squamous cell carcinoma is not infrequent, especially in the elderly, with over 1300 deaths from the disease in the UK (CRCUK figures for 2016)
- There is no established palliative chemotherapy for metastatic/inoperable cutaneous squamous cell carcinoma, so patients are usually treated with head and neck platinum containing regimens.
- Platinum containing regimens are toxic, especially in the elderly, and have limited effectiveness against cutaneous squamous cell carcinoma.
- The phase II results of cemiplimab in treating cutaneous squamous cell carcinoma are unprecedented and make the drug a potential game changer for the management of metastatic/inoperable disease.

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

Patient expert statement

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

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 conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- 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 10 pages.

About you	
1.Your name	**Clair McGarr**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ **X** a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ **X** other (please specify): A Skin Cancer Specialist Nurse and board member BASCSN
3. Name of your nominating organisation	BASCSN
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ **X** no, they didn't ☐ I don't know
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)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **X** other (they didn't submit one, I don't know if they submitted one etc.)

6. 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
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ **X** I have other relevant personal experience. Please specify what other experience: I look after patients with the condition ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with unresectable or advanced SCC is challenging – the disease can often be visible and can result in patients isolating themselves from social interaction. Physically it can result in unpleasant foul smelling wounds requiring sometimes multiple daily dressings, depending on the location of the disease it can also cause pain. Patients are often older and may have other conditions that impact on their ability to manage their condition. In the younger population patients are often very well except for their skin cancer but the visual nature of their disease often results in them retreating from their normal daily lives. Caring for a relative with this condition can be physically and emotionally draining. Palliation can be difficult and progression of disease is unpredictable leaving patients feeling like they are living on borrowed time never knowing when the disease might progress. Carers in particular find it difficult to deal with the uncertainty and the feeling of not being able to help.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There is a lack of treatment options for patients when surgical options are exhausted
10. Is there an unmet need for patients with this condition?	In general, we do need more treatment options and it is an area of unmet need currently
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Patients are aware that SCC in other cancer sites seems to respond well to immunotherapy and there is a lack of evidence that current chemotherapy options are effective. The advantages would be that treatment on offer would be more likely to be effective.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Patients are aware that there are side effects associated with immunotherapies as there are with any cancer treatments.
Patient population	
13. Are there any groups of patients who might benefit	No

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
15. Are there any other issues that you would like the committee to consider?	The numbers of patients with advanced cutaneous SCC are small but growing, given that SCCs of other types of cancers tend to respond to immunotherapy this seems like a sensible way forward.
Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For	

example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- cSCC is difficult to manage once surgical / radiotherapy options are exhausted
- unresectable and advanced cSCC is physically, emotionally and socially debilitating
- The current treatment options are limited

- There is unmet need in this group of patients
- It seems likely that cSCC would respond well to immunotherapies based on experience of SCC in other sites

Thank you for your time.

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NHS England submission in February 2019 for the technical engagement meeting of the NICE appraisal of cemiplimab in metastatic/locally advanced cutaneous squamous cell carcinoma

1. Cemiplimab has very clear activity in the management of patients with locally advanced or metastatic squamous cell carcinoma of the skin. It has a high response rate as evidenced by studies NCT 02383212 NCT 02760498 (overall response rate was the secondary and primary endpoints in these 2 studies, respectively). Cemiplimab impacts on progression dree survival but follow up is very immature.
2. There are very many and great uncertainties as to the clinical and cost effectiveness of cemiplimab in cutaneous squamous cell carcinoma (CSCC).
3. The first uncertainty is that the median duration of follow-up in the selected cohort in the phase II trial of cemiplimab is very short at only [redacted] months.
4. The second uncertainty is that the company has used different types of dosing, different treatment schedules and different treatment durations of cemiplimab in its studies and within its studies. The phase 1 study which also contributes some of the clinical efficacy results in the company's submission had a maximum treatment duration of 48 weeks and used weight-based dosing of cemiplimab. The main clinical evidence in the Sanofi submission was from 2 cohorts of the phase II EMPOWER study in patients treated with cemiplimab at a dose of 3mg/Kg every 2 weeks for a maximum treatment duration of 96 weeks. A third cohort in the EMPOWER cemiplimab phase II study was treated with the 350mg flat dose and 3-weekly schedule of cemiplimab and this was for a maximum of 54 weeks. The results of this third cohort have not been reported yet this is the dose and schedule that is expected to be licensed by the EMA (although it is not known as to the likely recommended treatment duration and whether this will be for 48 weeks or 54 weeks or 96 weeks or for an open duration). The FDA's license is for cemiplimab to be used until disease progression or unacceptable toxicity. NHS England notes the sensitivity of the cost effectiveness analyses according to maximum treatment duration.
5. The third uncertainty is that follow-up is so short that the median durations of progression free survival and overall survival have not been reached in a disease in which the company expects NICE's end of life criteria to apply.
6. The fourth uncertainty is that follow-up is short and therefore there must be caution in assessing toxicity for a drug that is expected to have uncommon but potentially serious toxicities which may not be manifest early in the treatment period (pneumonitis, hepatitis, nephritis, colitis and endocrinopathies).
7. The fifth uncertainty is that the population with which cemiplimab is being compared (those treated with combination chemotherapy in the Jarkowski study) numbered only 17 patients. NHS England notes that about 25% of patients were alive at 2 years in the Jarkowski comparator chemotherapy population which contrasts with the 5% figure given to Sanofi at one of its Advisory Boards.
8. The sixth uncertainty is the duration of treatment effect which to its credit Sanofi has modelled according to various scenarios.
9. The seventh uncertainty is the sensitivity of the economic model to the extrapolation of survival. This is not surprising given the short duration of follow up.
10. NHS England notes that the only clinical evidence for the efficacy and toxicity of cemiplimab is in patients of ECOG performance status PS 0 or 1 ie a fit group and patients in which a

platinum-based chemotherapy option would be possible in current pratice. It would not wish to commission the use of cemiplimab in patients of ECOG performance status greater than 1 without robust evidence that it was safe for patients to be treated.

11. NHS England is aware of the long term risk of cutaneous malignancy as a side-effect of chronic immunosuppression, particularly for anti-rejection therapy for previous solid organ transplants. Cemiplimab has strong biological plausibility for its mode of action reversing the immunosuppression in such patients and NHS England notes that patients with these conditions were excluded from the cemiplimab clinical trials.
12. In view of the very many uncertainties in the clinical and cost effectiveness of cemiplimab, NHS England regards cemiplimab for the treatment of CSCC as a very good candidate for the CDF provided that a) continued and sustained follow- up of the patients in the phase I and II studies is assured and includes the 350mg flat dosed 3-weekly schedule cohort 3 in the EMPOWER study and b) cemiplimab demonstrates plausible cost effectiveness in this indication.

[redacted]

Chair NHS England Chemotherapy Clinical Reference Group and CDF National Clinical Lead for the Cancer Drug Fund

February 2019

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma
Report version post factual accuracy check

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Date completed 28th February 2019

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Declared competing interests of the authors and clinical advisors

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Rider on responsibility for 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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Contributions of authors

Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanne Lord critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jill Colquitt critically appraised the clinical effectiveness systematic review and drafted the report; Emma Loveman critically appraised the clinical effectiveness systematic review and drafted the report; David Scott critically appraised the indirect treatment comparison and drafted the report; Geoff Frampton critically appraised the clinical effectiveness systematic review, drafted the report, project managed the report and is the project guarantor.

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LIST OF ABBREVIATIONS

AE(s)	Adverse event(s)
AIC	Akaike information criterion
BCC	Basal cell carcinoma
BNF	British National Formulary
BSC	Best supportive care
CAA	Commercial access agreement
CHMP	Committee for Medicinal Products for Human Use
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
DIC	Deviance information criterion
DOR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EPAR	European Public Assessment Report
ERG	Evidence Review Group
EQ-5D	EuroQol 5-Dimension
FDA	Food and Drug Administration
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
laBCC	Locally advanced basal cell carcinoma
laCSCC	Locally advanced cutaneous squamous cell carcinoma
MAIC	Matched adjusted indirect comparison
mBCC	Metastatic basal cell carcinoma
mCSCC	Metastatic cutaneous squamous cell carcinoma
NOS	Newcastle-Ottawa Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OS	Overall survival
ORR	Objective response rate
PAS	Patient access scheme
PD	Progressed disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PF	Progression free

PFS	Progression free survival
PH	Proportional hazards
PR	Partial response
PSSRU	Personal Social Services Research Unit
q2w	Once every two weeks
q3w	Once every three weeks
QALY	Quality adjusted life year
QoL	Quality of life
RCT(s)	Randomised controlled trial(s)
SAE(s)	Serious adverse event(s)
SCC	Squamous cell carcinoma
SD	Stable disease
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
STC	Simulated treatment comparison
TEAE(s)	Treatment emergent adverse event(s)
TTD	Time to treatment discontinuation

SUMMARY

Scope of the company submission

The company's submission (CS) is consistent with the NICE scope. However, no studies of best supportive care, which is a specified comparator in the scope, are available. The company has employed data from studies of chemotherapy and epithelial growth factor receptor (EGFR) inhibitors as proxies for best supportive care in their economic model.

The studies providing evidence of the effectiveness of cemiplimab in the CS employed a weight-based regimen of cemiplimab administered every 2 weeks, whereas the company's anticipated marketing authorisation is for a fixed dose administered every 3 weeks. Whilst the effectiveness evidence provided by the company is for the weight-based regimen, their economic model uses the fixed-dose regimen. The company argue that the two dose regimens result in similar rates of steady-state exposure to cemiplimab, based on pharmacokinetic simulation modelling.

Summary of the submitted clinical effectiveness evidence

The clinical effectiveness evidence for cemiplimab in advanced cutaneous squamous cell carcinoma (CSCC) is relatively limited and immature, provided by one first-in-human phase I study and one phase II non-randomised multi-cohort study. Analyses of survival outcomes are based on a pooled 'full analysis set' of 108 patients from both studies, with median follow-up of 8.9 (range 8.8 to 15.9) months at the latest available data cut-off. Median overall survival (OS), median progression-free survival (PFS), and median duration of response had not been reached. The overall response rate was [redacted].

No studies have directly compared cemiplimab against either the chemotherapy or best supportive care comparators. The company therefore conducted a systematic review to identify any studies of chemotherapy or best supportive care that could be included in an indirect treatment comparison. Only one relevant study of chemotherapy, and no relevant studies of best supportive care, were identified. The chemotherapy study is limited in being a retrospective chart review comprising only 18 relevant patients.

The company ran indirect treatment comparisons using three approaches: a simulated treatment comparison (STC), a matched-adjusted indirect comparison (MAIC), and a basic unadjusted, 'naïve' comparison. These compared cemiplimab individual patient data from the

pooled phase I and phase II studies against aggregate published data from the chemotherapy study. Both the STC and MAIC approaches account for inter-study heterogeneity by adjusting the population characteristics of the cemiplimab studies to match those of the chemotherapy study. A fundamental assumption of these approaches is that all prognostic factors for the outcomes have been included as covariates. In practice, due to limitations in the published chemotherapy study, only two prognostic factors could be adjusted for. A further important assumption is that the "target study", i.e. the chemotherapy study that provides the covariates for matching, is reflective of patients in real-world clinical practice. The chemotherapy study is not ideal in this respect, as it was conducted in the USA and very few clinical details are reported. Due to limitations in the evidence, both the company and ERG agree that results of the indirect treatment comparison are highly uncertain. Nevertheless, results from the naïve (unadjusted) comparison and the STC are used to inform the company's economic model.

Summary of the submitted cost effectiveness evidence

The CS includes:

i) a review of published economic evaluations of treatments for people with advanced CSCC
ii) An economic evaluation undertaken for the NICE STA process, comparing cemiplimab with chemotherapy and BSC for people with advanced CSCC who are not candidates for curative surgery or curative radiotherapy.

The company conducted a systematic search of the literature to identify economic evaluations of treatments in patients with CSCC and either locally advanced disease not suitable for surgery, or nodal or distant metastases. The search identified one published cost-effectiveness study. The company concluded that this study was not relevant to this appraisal as it did not separate patients with CSCC from those with basal cell carcinoma.

The company developed a conventional three state partitioned survival model to evaluate the cost-effectiveness of cemiplimab compared to chemotherapy and BSC in patients with CSCC. The model consists of three health states: pre-progression, progressed disease and death. Patients start in the progression-free state from where they can transition to the post-progression state or die. The distribution of the cohort between the health states at each time point is estimated using a set of PFS and OS curves for each intervention:

- The proportion of the cohort in the death state increases over time according to time-varying treatment-specific death rates defined by the OS curve or general population mortality (whichever is the higher).
- The proportion of the cohort in the progression-free state decreases over time in line with the treatment-specific time-varying hazard rates, defined by the minimum of PFS and OS.
- The residual proportion of the cohort in the post-progression state is defined by the difference between the proportion of patients alive and the proportion of patients in the pre-progression state at each point in time.

Other key features and assumptions of the model are listed below:

- Model cycle: monthly with half cycle correction.
- Time horizon: 30 years in the base case.
- Duration of treatment: For cemiplimab, treatment duration was similar to PFS. For chemotherapy, treatment duration was for 6 three-week treatment cycles.
- Treatment stopping rule: Maximum of 22 months treatment with cemiplimab
- Persistence of treatment effects: Cemiplimab PFS and OS hazards set equal to chemotherapy hazards 3 years from baseline
- Adverse events: One-off utility decrements and costs for grade 3 and 4 AEs with >=5% incidence for any study
- Utility and QALY calculations: EORTC-QLQ C30 values from phase II cemiplimab study mapped to EQ-5D-3L using a published algorithm
- Health resource use and costs: Resource use assumptions from clinical advisory group. Unit costs from published sources at 2016/17 prices.
- Discounting: 3.5% per year for costs and QALYs.
- Uncertainty: the model allows for exploration of uncertainty over input parameters using deterministic sensitivity analysis; scenario analyses varying selected model assumptions; and probabilistic sensitivity analysis (PSA) to estimate the joint effects of parameter uncertainty on the estimated costs and QALYs.

Summary of the robustness of the submitted evidence

Strengths

- The company has explored reasonable alternative approaches for conducting the indirect treatment comparison and they admit that the clinical effectiveness evidence is highly uncertain.
- The baseline patient characteristics from the clinical studies used in the company's base case are reasonably reflective of the relevant population seen in the NHS.
- The company conducted a comprehensive search for economic evaluations related to the decision problem, with appropriate eligibility criteria. Their findings are well-documented.
- The comparators in the company model reflect the NICE scope: chemotherapy (cisplatin in combination with 5-fluorouracil) and best supportive care. In the base case, the same clinical effectiveness data is used for both the comparators. The CS also presents a scenario analysis with proxy data for BSC from pooled EGFR inhibitor studies.
- The company follow a standard modelling approach adopted in oncology appraisals, using a simple three-state partitioned survival model.
- The company modelling approach and base case assumptions are reasonable and transparent. The CS gives a realistic view of the limitations of the evidence base and a fair discussion of the uncertainties. The base case uses relatively conservative assumptions and decisions are based on precedent where available, albeit with a few exceptions.
- The company adheres to the ISPOR guidelines for validating economic evaluations.

Weaknesses and Areas of uncertainty

The key limitation in the current technology appraisal is that the clinical effectiveness of cemiplimab is highly uncertain due to the limited, immature, data that are available. There are various sources of uncertainty and it is important to bear in mind that these are not captured in the statistical variance measures such as credible intervals or confidence intervals that accompany the statistical outputs.

- The comparator study included only 18 relevant patients; these are unlikely to be representative of the full spectrum of patients eligible for treatment. The study was conducted in the USA and it is unclear how relevant the comparator study is for patients presenting for advanced CSCC therapy in the NHS.

- The comparator study was retrospective and so might be biased.
- The ITC could only include two of 12 prognostic covariates identified as potentially important by the company and experts.
- The MAIC method of ITC further reduces the already small effective sample size.
- Naive comparisons are inadvisable as effectiveness outcomes are highly likely to be confounded with population differences between the studies.
- The ERG considers that the current evidence base is too weak to draw reliable conclusions about cost-effectiveness. We do not believe that the uncertainty is fully reflected in the company's sensitivity and scenario analyses.
- The long-term effects of cemiplimab are currently unknown
- The company report a well-structured process to fit and select PFS and OS survival curves for the economic model. Nevertheless, it is difficult to draw conclusions about goodness-of-fit or plausibility of the extrapolations.
- Best supportive care is the only treatment option for patients who cannot tolerate chemotherapy. It is not possible to draw meaningful conclusions about the cost-effectiveness of cemiplimab for these patients in the absence of information about their current rates of progression and survival.
- There is limited data to support estimates of the incidence of adverse events for people with advanced CSCC treated with cemiplimab and chemotherapy. Problems with the company's approach mean that modelled AE-related costs and QALY loss are likely to be underestimated and may be biased in favour of cemiplimab (due to the omission of long-term and immune-related effects).
- The results obtained from the company's method of estimating utility from patient-reported EORTC QLQ-C30 data, mapped to EQ-5D-3L UK tariff values are uncertain due to the very small sample size, short follow-up and additional uncertainty over the mapping parameters. Secondly, the company's use of a fixed pre-progression utility in the model that does not decline with age is inappropriate, exaggerating the QALY gain from delayed progression attributed to cemiplimab.
- The company use a fixed dose regimen to cost cemiplimab in their economic analysis. Whilst this is consistent with the proposed marketing indication, it is inconsistent with the clinical effectiveness data used in the model, which relates to a weight-based regimen.

Summary of additional work undertaken by the ERG

We applied the following corrections to the company model:

- Pre-progression utility set equal to general population estimates (adjusted for age).
- Fixed decrement used to estimate post-progression utility.
- Standard errors for health state utilities reduced (model included standard deviations).
- Corrections to unit costs and uprated to 2018 prices.

The deterministic base case results with ERG corrections at the proposed CAA prices are shown in Table 1. The ICERs are higher than those reported by the company (CS Table 44 and 46):

- £49,155 compared with £43,740 for the comparison with chemotherapy;
- £52,539 compared with £46,239 for the comparison with BSC.

These increases are driven by both higher costs (due to uprating of unit costs to 2018 prices) and lower QALY gains (due to addition of age-adjustment for pre-progression utility), and are more pronounced for cemiplimab, because it is associated with longer predicted pre-progression and OS than the comparators.

Table 1: Cost effectiveness: ERG corrected company base case, deterministic (proposed CAA price for cemiplimab)

			Cemiplimab versus comparator		
	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	**Pairwise** ICER**s**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£52,539
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£49,155
Cemiplimab	[redacted]	[redacted]			

ERG Scenario analysis around these corrected base case results showed that:

- Results are sensitive to OS extrapolations: e.g. lower ICERs when the Gompertz is used for cemiplimab and comparators; and higher ICERs with log-normal. However, results are not sensitive to changes in PFS distributions.
- The model is highly sensitive to the assumed duration of treatment and persistence of benefits, with ICERs below £50,000 per QALY when we assume only 1 year of treatment

and persistence of effects for a further year, to over £80,000 per QALY if we do not limit the duration of treatment pre-progression or the assumed duration of effects.

- Changes to the clinical data source lead to some large changes in ICERs. Excluding the phase I cemiplimab study data increases ICERs above £60,000 per QALY. The STC data and elicited estimates from experts reduce the ICER estimates.
- There is a modest increase in ICERs when the costs of cemiplimab are estimated for the weight-based regimen on which the clinical effectiveness data were based. As might be expected, this finding is sensitive to the mean weight of the population.
- Reducing health state resource use, and hence costs, causes a small reduction in estimated ICERs.
- There is a small reduction in ICERs if we assume a constant proportional reduction in utility, rather than a constant absolute reduction, following disease progression.

The ERG considers the current evidence base to be insufficient to draw reliable conclusions about comparative effectiveness, hence cost-effectiveness. We conducted a range of scenario analyses to address some of the uncertainty; however we do not believe the degree of uncertainty is fully reflected through these analyses. Given the limited data, we chose not to present a single ERG 'base case'. Instead, we outline below two scenarios reflecting sets of optimistic and pessimistic assumptions drawn from what we consider to be plausible options (see Table 2). These scenarios should be treated with caution, as they do not reflect the absolute range of uncertainty associated with the existing evidence.

The results of the ERG plausible scenarios are presented in Table 3. As expected, the results obtained from the ERG scenarios give a wide range for the ICERs comparing cemiplimab versus chemotherapy and versus BSC. For cemiplimab versus chemotherapy, the ICER ranges from £35,078 (optimistic scenario) to £73,155 (pessimistic scenario) whereas the ICER varies between £32,783 (optimistic scenario) and £76,376 (pessimistic scenario) when cemiplimab is compared with BSC. Such wide variations in results indicate that there is not enough information to draw meaningful cost-effectiveness conclusions as to whether cemiplimab provides good value for money for the NHS at a willingness-to-pay threshold of £50,000 per QALY.

Table 2 ERG preferred modelling assumptions

		Company base case	ERG pessimistic	ERG optimistic
Clinical data	BSC	Jarkowski study	Jarkowski study	Pooled EGFR studies
OS	Cemiplimab Chemotherapy/ BSC	Lognormal Gompertz	Lognormal Lognormal	Gompertz Gompertz
Stopping	Cemiplimab	22 months	24 months	22 months
Effect cap	Cemiplimab	36 months	36 months	60 months
Adverse events	Cemiplimab	One off	Annual during treatment	One off
Drug costs	Cemiplimab Chemotherapy	Fixed dose 6 cycles	Weight-based 3 cycles	Fixed dose 3 cycles
Utilities		Longworth mapping	NICE TA473[57]	Longworth mapping
Health state resource use		CS Tables 35 & 37	Reduced resource use pre-progression (ERG scenario)	

Table 3 ERG scenarios, deterministic (proposed cemiplimab CAA price)

	Comparator	Total cost	Total QALYs	Pairwise ICERs (cemiplimab vs comparators)
Company base case (ERG corrected)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£49,155
	BSC	[redacted]	[redacted]	£52,539
ERG optimistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£35,078
	BSC	[redacted]	[redacted]	£32,783
ERG pessimistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£73,155
	BSC	[redacted]	[redacted]	£76,376

1 INTRODUCTION TO THE ERG REPORT

This report is a critique of the company's submission (CS) to NICE from Sanofi on the clinical effectiveness and cost effectiveness of cemiplimab for treating people with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) in whom there is no curative local therapy. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the manufacturer by the ERG via NICE on 14th November 2018. A response from the company via NICE was received by the ERG on 3rd December 2018 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

The CS presents evidence on the clinical effectiveness and cost-effectiveness of cemiplimab (brand name Libtayo) for treating patients who have advanced CSCC. Cemiplimab is a human immunoglobulin monoclonal antibody that binds to the programmed death protein 1 (PD-1) receptor, blocking the engagement between PD-1 and its ligand PD-L1 on tumour cell surfaces. This has the effect of restoring T-cell signalling, enabling the immune system to recognise tumour cells which would otherwise evade detection. Cemiplimab is thus referred to as a PD-1 inhibitor. The dose regimen used in the evidence of clinical effectiveness of cemiplimab for advanced CSCC is a weight-based dose of 3 mg/kg, administered over 30 minutes by intravenous (IV) infusion once every 2 weeks. As discussed below (section 2.2), this differs from the dose regimen in the company's intended licence [redacted].

2.1 Critique of the company's description of the underlying health problem and overview of current service provision

2.1.1 The underlying health problem

The CS provides an accurate description of CSCC, and the epidemiology, prognosis and burden of the disease (CS section B.1.3). The population relevant to the NICE scope consists of patients with locally advanced CSCC (laCSCC) and patients with metastatic CSCC (mCSCC), although the company has grouped these together as one 'advanced CSCC' population of people with metastatic CSCC or locally advanced CSCC who are not candidates for curative

surgery or curative radiotherapy. Clinical experts advising the ERG agreed that this grouping is appropriate, as both types of CSCC are highly progressive with a poor outlook and would not differ in treatment. Pooling the laCSCC and mCSCC groups also increases the numbers of patients in the analysis. We believe that pooling these groups is appropriate for assessing the overall survival (OS) outcome. The statistical power calculations for one of the company's pivotal studies, reported in the interim clinical study report (CSR),[1] assume that response rates are higher for laCSCC than for mCSCC with currently available therapies, although the references cited in the CSR[1] to support this appear unclear (see section 3.1.6.2). Clinical experts advising the ERG suggested that there might be some differences in symptoms and HRQoL between the laCSCC and mCSCC groups, although empirical data are lacking (4.3.2.1). The NICE scope states that if the evidence allows, subgroups should be considered for people with mCSCC, and for people with laCSCC for whom there is no curative local therapy. The CS reports these subgroups in addition to the advanced CSCC population analyses.

We note that definitions of laCSCC and mCSCC can vary. Patients are often referred to as having either "locoregional" or "metastatic" CSCC, but these categories can overlap depending on the classification system employed. The locoregional disease category always includes patients with uncontrolled/unresectable local disease, whilst the metastatic disease category always includes those with distant metastases. Differences in classification relate to whether patients whose disease has spread to local lymph nodes are included in the locoregional category or the metastatic category. As such, patients with nodal involvement could be classified either as having laCSCC or mCSCC. The CS explains that the classification of mCSCC and laCSCC differed between the company's pivotal phase I and phase II studies (CS section B.2.3.1.3). Patients who had regional nodal metastases were enrolled in the laCSCC cohort in the phase I study but were classified as having mCSCC in the phase II study. For the company's combined analysis of the phase I and phase II studies, referred to as an "integrated analysis" (see section 3.1.3 below), the company has reclassified patients in the phase I study to be consistent with the definitions of mCSCC and laCSCC employed in the phase II study. The ERG agrees that the company's approach is appropriate to ensure comparability of the phase I and phase II study populations in their integrated analysis.

2.1.2 Current service provision

The CS briefly summarises the treatment pathway for patients with CSCC in the UK (CS Figure 3). Clinical experts advising the ERG agreed that this summary is accurate, with the minor

exception that, in the event of disease recurrence, the multidisciplinary team (MDT) that the patient would be referred to would be a specialist MDT. The positioning of cemiplimab in the treatment pathway is for patients with advanced CSCC who are not candidates for surgery or radiotherapy and who would currently receive systemic treatment and/or best supportive care (BSC). There are currently no licensed systemic treatments for this indication although clinicians may use unlicensed platinum-based chemotherapy (usually cisplatin and 5-flurouracil). Our clinical advisors agree with the CS that other potential treatments, such as EGFR inhibitors, interferon-alfa, or oral retinoic acid, are unlikely to be used in the NHS in England. The company state that their UK clinical advisory board suggested that approximately 75% of people with advanced CSCC are not suitable for chemotherapy and would receive BSC. Clinical experts advising the ERG suggested that some (proportion uncertain) of these people could be potential candidates for immunotherapy.

2.2 Critique of the company's definition of the decision problem

The company's decision problem is consistent with the NICE scope in terms of the population, comparators (although no evidence was found for BSC) and outcomes. The intervention, cemiplimab, is also in line with the NICE scope. However, the evidence included in the CS is based on a different cemiplimab dosing regimen (weight-based 3 mg/kg every 2 weeks) than the anticipated marketing authorisation (fixed dose 350 mg every 3 weeks). The company states that the fixed-dose regimen was introduced over the course of the cemiplimab development programme and this is expected to be the licenced dose (CS section B.2.13.1). The company argue, based on pharmacokinetic (PK) simulation modelling, that overall exposure to cemiplimab would be similar for the two regimens. Details of the PK modelling are not reported in the CS but were provided in clarification question response A20. Although these analyses suggest that both dose regimens would lead to similar cemiplimab exposure, the ERG has some concerns about the analyses, particularly regarding the small sample sizes involved and whether the analyses (which included patients with any solid tumours) were based on an appropriate reference population for drug exposure in advanced CSCC. These issues are summarised briefly in Appendix 1. The CS acknowledges that there is some uncertainty associated with the PK modelling. The company states that [redacted]

The company's decision problem is as follows:

Population: People with laCSCC or mCSCC who are not candidates for curative surgery or curative radiotherapy.

Intervention: Cemiplimab.

Comparators: BSC; chemotherapy (such as platinum based chemotherapy and fluorouracil).

Outcomes: progression-free survival (PFS); overall survival (OS); response rate; duration of response; adverse effects; health-related quality of life (HRQoL).

Other considerations: the company provides evidence for the subgroups specified in the NICE scope: people with mCSCC, and people with laCSCC who are not candidates for curative surgery or curative radiotherapy.

Equality

The company notes that patients with advanced CSCC are often older, with average age in the cemiplimab studies around 70 years (age is a protected characteristic under the Equality Act 2010).

> **ERG conclusion:** The company's decision problem is consistent with the NICE scope, although no evidence was identified for the BSC comparator. The dose regimen in the CS differs from that of the company's anticipated marketing authorisation. The company conducted PK modelling do demonstrate the equivalence of the two regimens but this approach has some uncertainties (Appendix 1).

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's approach to systematic review

3.1.1 Description of the company's search strategy

The company conducted the following searches:

- Clinical effectiveness (CS section B.2.1; detail in CS Appendix D.1).
- Economic evaluations (CS section B.3.1; detail in CS Appendix G).
- HRQoL, (CS section B.3.4.1; detail in CS Appendix H).
- Costs and resources (CS section B.3.5; detail in CS Appendix I)

The company reports that all searches were run in October 2017 and updated in September 2018, apart from the costs and resources search which was run in June 2018.

The search strategies and the range of databases searched are clearly reported for these four searches and we consider them to be appropriate. The CS does not specifically mention searching ongoing trials databases, although links to clinicaltrials.gov appear in the CS reference list, suggesting some ongoing research may have been captured.

We searched the WHO International Clinical Trials Registry Platform, NIHR UK Clinical Trials Gateway and clinicaltrials.gov to check whether further clinical studies on Cemiplimab were underway. We also conducted searches to identify any recent relevant comparator studies, e.g. including current palliative therapies, chemotherapeutic agents such as platinum therapies, and BSC in the treatment of CSCC, using the clinical trial databases mentioned above and additionally in Embase, Medline and Pubmed. We also asked four clinical experts whether they were aware of any further relevant sources of evidence not already identified by the company; and we contacted the administrators of the National Disease Registration Service for any relevant data on patients with advanced CSCC that might be available. Despite these searches, no key additional evidence relevant to the current technology appraisal was identified.

Given that the search for costs and resources is around 4 months out of date we reran this search in Medline. No further relevant evidence was identified.

ERG conclusion: The company's searches were generally up-to-date and fit for purpose and the ERG and clinical expert advisors did not identify any key missing studies.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The CS reports inclusion and exclusion criteria for an indirect treatment comparison (ITC) of cemiplimab and potential comparator therapies (CS Appendix Table 7). The population eligibility criteria are consistent with the NICE scope.

Due to the anticipated lack of evidence, the intervention criteria were initially broader than the NICE scope, permitting any intervention other than surgical interventions for laCSCC to be included. Interventions were then restricted during a feasibility assessment for the ITC (CS section D.1.3.1). Studies on the following interventions were considered not relevant at the feasibility assessment step and were excluded: surgery for regional mCSCC; radiotherapy for laCSCC; oral retinoic acid with subcutaneous interferon α2-a; electro-chemotherapy; dacomitinib; panitumumab; and epithelial growth factor regulator (EGFR) inhibitors (e.g. cetuximab, gefitinib and erlotinib). These exclusions bring the interventions in line with the NICE scope, and clinical experts advising the ERG agreed that the exclusions are appropriate since these interventions are not generally used in current UK clinical practice for people with advanced CSCC.

The list of eligible outcomes in CS Appendix Table 7 is broadly consistent with the NICE scope. The outcomes are more specific than those stated in the scope (e.g. disease-specific OS, different categories of responses, and different classes of adverse events are specified as eligibility criteria), although the ERG believes these are generally appropriate outcomes.

The CS provides a PRISMA flow diagram (CS Figure 4, duplicated in CS Appendix Figure 1) showing the numbers of references and studies that were excluded during the initial stage of screening (i.e. those screened against the eligibility criteria reported in CS Appendix Table 7, prior to the feasibility assessment). A list of excluded studies with reasons for exclusion is not reported in the CS, but has been provided by the company to the ERG on request (separately to the formal clarification process). The CS does not present a flow diagram for the selection of studies during the feasibility assessment step. The reasons for excluding studies at the feasibility assessment are explained narratively in CS section D.1.3.1 but not all of the studies

have been referenced so the rationale for some of the exclusions is not clear. Details of the excluded studies have been provided by the company in clarification question response A2.

The CS does not discuss the possibility of selection bias arising during the eligibility screening process. Two reviewers independently conducted the initial screening (CS section D.1.2) which is good practice to minimise the risk of bias, but the number of reviewers involved in the feasibility assessment is not reported. As the eligibility criteria were refined during the review process there is potential for bias. However, the ERG considers this unlikely as we have not identified any obvious omissions of key studies or the inclusion of clearly irrelevant studies.

> **ERG conclusion:** The company employed a combination of pre-specified and post-hoc eligibility criteria, so there is a risk of selection bias. However, the ERG and clinical expert advisors believe the company has included all available relevant cemiplimab and comparator studies.

3.1.3 Identified studies

The company's searches did not identify any randomised controlled trials (RCTs) of cemiplimab or of relevant comparators. The evidence to support the clinical effectiveness of cemiplimab is provided by two non-comparative, company-sponsored, multicentre studies. These studies, which are summarised in CS Tables 3 and 4, are a phase I study (NCT02383212, also referred to as study 1423) and a phase II study (NCT02760498; EMPOWER-CSCC-1) and they include populations and outcomes which are consistent with the company's decision problem described above (section 2.2). We refer to these studies throughout this report as the phase I study and the phase II study.

The phase I study is an ongoing study evaluating the safety (primary outcome) and efficacy (secondary outcome) of cemiplimab in adults with advanced solid tumours. The expansion phase of the study had 24 cohorts representing a wide range of solid tumours and combinations of therapy (ceplimimab monotherapy or combination therapy) and in total 398 participants were included.[2] Only one of these expansion cohorts is relevant to the current technology appraisal, comprising 26 participants with advanced CSCC (16 with mCSCC and 10 laCSCC). These patients had at least one measurable lesion, were not candidates for surgery, and they received intravenous (IV) cemiplimab monotherapy at a weight-based dose of 3 mg/kg, administered over 30 minutes once every 2 weeks for up to 48 weeks. As noted above (section 2.2), this

weight-based regimen differs from the company's anticipated marketing authorisation, which is for IV cemiplimab 350mg once every three weeks.

The phase II study is an ongoing study of the efficacy and safety of cemiplimab in adults with advanced CSCC, who had at least one measurable lesion and were not candidates for surgery. The primary outcome is overall response rate (ORR). The study originally had two cohorts, mCSCC (n=59) and laCSCC (n=55) (referred to in the CS as group 1 and group 2 respectively). Participants in these groups received weight-based cemiplimab monotherapy, according to the same regimen as in the phase I study described above, for up to 96 weeks. A third cohort of patients with mCSCC (referred to in the CS as group 3) was added after group 1 enrolment had been completed and this cohort is still recruiting (n=23 at the latest data cut-off). In contrast to groups 1 and 2, the third group received a fixed-dose regimen of IV cemiplimab monotherapy, in line with the company's anticipated marketing authorisation, i.e. 350mg once every three weeks.

No clinical effectiveness outcomes are reported in the CS for the 23 patients in group 3 of the phase II study, although these are the patients who most closely match the company's anticipated licence in terms of the dose regimen. The ERG requested data for these 23 patients but the company confirmed that at the time of the latest (October 2017) data cut-off there was inadequate follow-up for these patients ([redacted]) and no centrally reviewed data were available (clarification question response A10).

As described in more detail below (section 3.1.5), patients' response to therapy in both studies was assessed by imaging patients every 8 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Effectiveness results were assessed by independent central review.

For the company's analyses, effectiveness and safety outcomes from the phase I and phase II studies were pooled, and this is referred to in the CS as the "integrated analysis". The rationale and implications for pooling the studies are discussed in section 3.1.6 (clinical experts advising the ERG considered the approach appropriate).

The CS reports key baseline characteristics of the total participants in each of the two studies and for the total integrated analysis population (CS section B.2.3.2), and these are summarised below in Table 4. The CS also reports key baseline characteristics for each of the mCSCC and

laCSCC groups within the phase I and phase II studies and in the integrated analysis (CS Appendix Table 44). We have summarised these characteristics below, for mCSCC participants in Table 5 and for laCSCC participants in Table 6.

The company refers to the integrated analysis population as the "full analysis set". This includes all laCSCC and mCSCC patients in the phase I and phase II studies apart from 55 participants in the phase II study. These 55 excluded participants were 32 in the phase II study laCSCC group who did not complete 9 months of follow up and 23 in the phase II study who received fixed-dose cemiplimab (group 3). The contribution of each of the mCSCC and laCSCC groups to the full analysis set (N=108) is clearly illustrated in CS Figure 7. We discuss the analysis populations in relation to the statistical analysis approach further below in section 3.1.6.3.

Overall, the characteristics of participants with advanced CSCC in the full analysis set of the phase II study (i.e. those who were included in the integrated analysis: N=82) appear similar to those of the full phase II study population (N=137) (Table 4). Some differences are evident between the overall advanced CSCC populations in the phase I and phase II studies. For example, a higher proportion of phase I than phase II study participants had received prior cancer related systemic therapy, prior cancer related radiotherapy, and [redacted]. However, it is unclear how meaningful these relatively small differences are given the small sample sizes involved.

Table 4 Key baseline characteristics for the integrated analysis and individual studies

Characteristic		Integrated analysis (N=108)	Phase I study (N=26)	Phase II study	
				Full analysis set (N=82) [a]	All participants (N=137) [b]
Male, %		[redacted]	80.8	[redacted]	[redacted]
Median age (range)		[redacted]	72.5 (52-88)	[redacted]	[redacted]
Weight, mean kg (SD)		[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, %	0	[redacted]	38.5	[redacted]	[redacted]
	1	[redacted]	61.5	[redacted]	[redacted]
Prior cancer related systemic therapy, %		[redacted]	57.7	[redacted]	40.1
[redacted]			[redacted]	[redacted]	
Number of regimens at baseline, %	0	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]
	≥2	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Integrated analysis (N=108)	Phase I study (N=26)	Phase II study	
			Full analysis set (N=82) [a]	All participants (N=137) [b]
Prior cancer related surgery, %	[redacted]	92.3	[redacted]	92.0
Prior cancer related radiotherapy, %	[redacted]	[redacted]	[redacted]	[redacted]

Sources: Based on CS Table 5; full analysis set data are from clarification question response A5; prior monoclonal antibody therapy data are from the CSRs. Blank cells indicate data not reported.
[a] Full analysis set excludes 23 mCSCC patients who received fixed-dose cemiplimab and 32 laCSCC patients who did not complete 9 months of follow up.
[b] All participants in the study, irrespective of their dose regimen, follow up and availability of clinical effectiveness outcomes.
[redacted].

Comparison of the characteristics of participants with mCSCC and laCSCC is limited by the very small sample size of the laCSCC group. For the integrated analysis (laCSCC n=33 and mCSCC n=75) Table 5 and Table 6 show that a smaller proportion of laCSCC than mCSCC participants had prior cancer-related systemic therapy ([redacted]) as well as slightly lower proportions with prior cancer-related radiotherapy, ECOG performance status of 1, weight, age, and male sex.

Characteristics of the participants in group 3 of the phase II study who received fixed-dose cemiplimab and were excluded from the integrated analysis were provided by the company in clarification question response A10 (not shown here). There are some differences between this small group (n=23) and the full analysis set of the phase II study, but no clear suggestion that the characteristics of the fixed-dose and weight-based dose mCSCC groups were substantially different.

The phase I and phase II studies are, in part, reported in a peer-reviewed publication (Migden et al. 2018)[3] (which reports the mCSCC groups only, as the time point for the primary analysis for the laCSCC population had not been reached). The ERG has cross-checked the information reported in the CS against the publication,[3] the CSRs for the phase I study[2] and phase II study,[1] a clinical overview,[4] a summary of clinical effectiveness,[5] a safety analysis summary,[6] and the draft Summary of Product Characteristics (SmPC)[7] which were provided by the company in their submission.

Both of the pivotal studies are currently ongoing and the CS confirms that [redacted].

Section B.2.11 of the CS also states that a retrospective chart review study is also ongoing and will provide further relevant data including OS, PFS and ORR outcomes for patients with advanced CSCC. The ERG requested further details of the chart review study, and the company has provided the eligibility criteria in clarification question response A11. The company proposes further data collection from these ongoing studies to allow fuller consideration of cemiplimab as an appropriate candidate for the UK Cancer Drugs Fund, to reduce uncertainty (CS Appendix O).

Table 5 Key baseline characteristics of mCSCC participants

Characteristic	Integrated analysis (n=75)	Phase I study (n=16)	Phase II study	
			Group 1, weight-based dose (n=59)	Group 3, fixed dose (n=23) [a]
Male, %	[redacted]	[redacted]	91.5	[redacted]
Median age (range)	[redacted]	[redacted]	71 (38-93)	[redacted]
Weight, mean kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, % 0	[redacted]	[redacted]	39.0	[redacted]
ECOG performance status, % 1	[redacted]	[redacted]	61.0	[redacted]
Prior cancer-related systemic therapy, %	[redacted]	[redacted]	55.9	[redacted]
[redacted]		[redacted]		
Prior cancer-related surgery, %	[redacted]	[redacted]	98.3	[redacted]
Prior cancer-related radiotherapy, %	[redacted]	[redacted]	84.7	[redacted]

Source: CS Appendix Table 44; prior monoclonal antibody therapy data are from the CSRs. Blank cells indicate data not reported.
[a] These participants were not included in the integrated analysis.
[redacted]

Table 6 Key baseline characteristics of laCSCC participants

Characteristic	Integrated analysis (n=33)	Phase I study (n=10)	Phase II study (n=55) [a]
Male, %	[redacted]	[redacted]	[redacted]
Median age (range)	[redacted]	[redacted]	[redacted]
Weight, mean kg (SD)	[redacted]	[redacted]	[redacted]

ECOG performance status, %	0 1	[redacted]	[redacted]	[redacted]
Prior cancer-related systemic therapy, %		[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	
Prior cancer-related surgery, %		[redacted]	[redacted]	[redacted]
Prior cancer-related radiotherapy, %		[redacted]	[redacted]	[redacted]

Source: CS Appendix Table 44. Blank cells indicate data not reported.
[a] Of these 55 participants, only 23 who completed 9 months of follow up were included in the integrated analysis.
[redacted]

We note that in addition to the differences in baseline characteristics, the phase I and phase II studies also differed in their exposure to cemiplimab and in their length of follow-up, both of which were longer in the phase I study (section 3.1.6.1).

> **ERG conclusion:** The clinical effectiveness evidence for cemiplimab comes from two non-comparative phase I and phase II ongoing studies with relatively small sample sizes (total N=108) and immature data. There appears to be some heterogeneity in the populations in the two studies, mainly relating to the extent of prior cancer-related therapy, and there were differences in the duration of cemiplimab exposure and follow-up, but uncertainty is high due to the small sample sizes.

3.1.4 Description and critique of the approach to validity assessment

The company provided a quality assessment of the two cemiplimab studies (CS Appendix Table 15) as well as a quality assessment of one relevant chemotherapy comparator study that they had included in their indirect treatment comparison, by Jarkowski et al. 2016[8] (CS Appendix Table 14). The selection of the Jarkowski study for the indirect treatment comparison, and the study's characteristics, are described below in section 3.1.7.1. The company also assessed the quality of four EGFR inhibitor studies[9-12] (CS Appendix Table 14). These studies were not included in the company's indirect treatment comparison but were used as a proxy for BSC in the economic analysis (as explained below in section 4.3.4.4).

The CS reports that since there were no RCTs of cemiplimab or comparators they used the Newcastle-Ottawa Scale[13] for non-randomised studies to assess study quality. No justification for this scale or interpretation of its results are provided by the company. The Newcastle-Ottawa

Scale addresses three domains of study "quality": selection, comparability, and ascertainment of outcomes, each with one or more criteria.[13, 14] A star (asterisk) is applied if the quality criterion is met. The Newcastle-Ottawa Scale is not commonly used in NICE appraisals and has several limitations.[14-17] Nevertheless, the ERG has checked the company's assessments using this scale provided for the cemiplimab studies and Jarkowski chemotherapy comparator study, and we have considered other key aspects of validity. A comparison of the company's and ERG's assessments for the cemiplimab and chemotherapy studies is provided in Appendix 2. We provide a brief summary of the EGFR-inhibitor studies and their validity in Appendix 3**.**

The ERG agrees that the cemiplimab studies have good internal validity (low risk of bias) in terms of ascertainment of exposure (treatment and doses received), assessment of outcomes (by independent central review), and attrition (no evidence of unintended withdrawals or missing outcomes data). In addition, the ERG considers that there is a low risk of bias in the selection of participants due to the prospective, protocol-driven recruitment. However, although the company considers the length of follow-up to be appropriate, the ERG notes that not all outcomes could be ascertained in the follow-up period, and that both studies are ongoing and data are immature. In addition, external validity (representativeness of the cohort) is considered by the company to be appropriate, but the ERG notes that the population is non-UK and younger and fitter than in UK clinical practice (CS section B.2.5). In summary, the ERG believes that the key limitations of the cemiplimab studies are that they were single-arm studies (i.e. a design that cannot unequivocally exclude selection bias and establish a cause-effect relationship) and that follow-up was relatively short for the condition being investigated. Two of four clinical experts advising the ERG commented that whilst the follow-up was relatively short, it was sufficient to demonstrate a response to therapy. However, the ERG is concerned that the relatively short duration of follow-up would be insufficient to confirm long-term effects of cemiplimab.

The company rated the Jarkowski chemotherapy comparator study as being overall of good quality on the Newcastle-Ottawa Scale. However, the ERG considers that although this study had an adequate duration of follow-up, it is very small (N=18 patients received platinum chemotherapy) and at high risk of bias due to the retrospective selection of cases (Appendix 2). In addition, the generalisability is unclear due to the non-UK population, younger age, and higher proportion of trunk lesions than would be expected in NHS clinical practice, and the limited reporting of baseline characteristics.

ERG conclusion: The company assessed the quality of the cemiplimab and comparator studies but did not focus on validity (risk of bias). The main limitations of the cemiplimab studies are that they were single-arm non-comparative studies with short follow-up. The chemotherapy comparator study had a single arm, very small sample size and, being retrospective, a high risk of bias.

3.1.5 Description and critique of the company's outcome selection

The outcomes selected by the company are standard outcomes for oncology trials and are consistent with the outcomes listed in the NICE scope and the company's decision problem. The outcomes which inform the company's economic model are PFS and OS, (section 4.3.4), adverse events (section 4.3.6), and HRQoL (section 4.3.6). The CS presents all the key outcomes that are reported in the study publications and interim CSRs, with the exception of immunotherapy-related adverse events which are missing from CS Table 25 (the implications of this omission are discussed in relation to the economic analysis in section 4.3.6 below).

3.1.5.1 Response outcomes

The objective response rate (ORR), assessed by independent central review, was the primary outcome in the phase II study. Responses were determined separately for laCSCC and mCSCC patients, by three independent central review committees:

- An Independent Radiologic Review Committee (IRRC) provided assessments for mCSCC (group 1) patients in whom all response assessments were performed on radiologic scans according to RECIST 1.1 criteria.
- An Independent Composite Review Committee (ICRC) provided assessments for mCSCC (group 1) patients with externally visible lesions, on whom digital medical photography was performed and composite response criteria were used.
- An Independent Photographic Review Committee (IPRC) provided assessments for laCSCC (group 2) patients in whom the composite response was based on photographic assessment of externally visible lesions according to modified WHO criteria and assessment of radiologic data according to RECIST 1.1. The ICRC integrated all of the information provided by the IPRC and the IRRC for each laCSCC patient.

Response rate was a secondary outcome in the phase I study. The CS and interim CSR[2] state that “central review for efficacy was performed by two independent radiologists and an adjudicator if needed”, without further details.

Lesions that could not be measured according to RECIST v 1.1 criteria are referred to as nontarget lesions. Patients with only nontarget lesions were considered to have a noncomplete response or nonprogressive disease, unless there was disappearance of all lesions or unequivocal progression. Measurements that were obtained after disease progression were excluded.

The CS presents ORR results for the integrated analysis both for independent central review and (as a secondary outcome) investigator assessments, which is appropriate. The response outcomes reported in the CS are objective response rate (ORR), complete response (CR), partial response (PR) disease control rate (DCR), stable disease (SD), progressive disease (PD), duration of response (DOR), and time to response (TTR). These outcomes follow standard definitions, as specified in Appendix 3 of the Clinical Study Protocol (supplementary appendix to the study publication by Migden et al.[3]).

3.1.5.2 Survival outcomes

Survival outcomes followed standard definitions. Progression-free survival (PFS) was defined as the time from the start of treatment until the first date of recurrent or (radiographic) progressive disease or any-cause mortality. Overall survival (OS) was defined as the time from the start of treatment until any-cause mortality (NB: median PFS and OS were not reached in either the phase I or phase II studies or the integrated analysis; see section 3.3.2).

3.1.5.3 Health-related Quality of life (HRQoL)

HRQoL was assessed only in the phase II study, using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. The EORTC QLQ-C30 consists of 30 items which capture generic aspects of a patient’s HRQoL during the preceding week, divided into five functional scales (physical, role, cognitive, emotional, social), a global quality of life scale, three symptom scales (fatigue, pain, nausea/vomiting), and several single-item symptom measures (dyspnea, loss of appetite, sleep disturbance, constipation, diarrhoea,

financial difficulties). The EORTC QLQ-C30 has been demonstrated to have good construct validity in non-melanoma skin cancer[18] and is among the most widely-used cancer HRQoL instruments[19] and so the choice of this instrument is reasonable. The CS comments (CS section B2.6.4.1) that clinical experts at their UK advisory board agreed that although the EORTC QLQ-C30 is generally suitable for capturing quality of life data, it may not be as sensitive in capturing the anxiety and depression experienced by patients with advanced CSCC.

HRQoL scores from the EORTC QLQ-C30 range from 0–100, with higher scores in function scales representing a higher level of functioning, and higher scores in symptom scales indicating greater impairment. Minimum clinically important difference (MCID) values for improvement and deterioration in each of the EORTC QLQ-C30 subscales have been estimated for several different cancers (e.g. bone cancer,[20] brain cancer[21]) but as far as we are aware not specifically for skin cancer. The CS presents relatively few results from the EORCT QLQ-C30 but does refer to a potentially clinically meaningful change [redacted] (CS section B.2.6.4.1), citing Raman et al.[20] as the benchmark for what the company considered may be a clinically meaningful change. We note that the study by Raman et al.[20] (which reported MCID=9.4 for improvement in pain) was specifically on a population with bone cancer, and it is unclear how relevant this is to patients with advanced CSCC (possibly more relevant to those with bone metastases than those without). In addition, the baseline pain score in the phase II study [redacted] was [redacted] than in Raman et al. (mean 69.7)[20] and it is uncertain whether the reported MCID has the same clinical relevance at this baseline.

Given that HRQoL data were not collected using the EQ-5D, the company obtained estimates of the pre- and post-progression utility for patients with advanced CSCC, as required in their economic analysis, by mapping EQ-5D utility scores from the EORTC QLQ-C30 scores obtained in the phase II study (CS Appendix N). We provide a critique of the mapping process in section 4.3.6 below.

3.1.5.4 Adverse events

The safety analysis set was defined as all patients who received at least one dose of cemiplimab on or before the cut-off date defined for each study (CS section B.2.10). The categories of adverse events are not defined in the CS or interim safety summary,[6] although the study publication[3] states that severity of adverse events was graded according to National Cancer Institute Common Terminology criteria for Adverse Events, version 4.03.

The CS focuses on treatment-emergent adverse events (TEAEs), which are listed in detail (≥5% of any grade; ≥1 of grade 3/4/5 in any group), for the phase I study, phase II study, and integrated analysis (CS Table 13), and for two wider safety cohorts that included all patients who had received cemiplimab monotherapy ("Pool 2") and all patients who had received either cemiplimab monotherapy or combination therapy ("Pool 3") across both the phase I and phase II studies, which included patients in the phase I study with other non-CSCC solid tumours (CS Appendix F.2). Other types of adverse event are tabulated in the CS only as the overall frequencies of total events, for serious adverse events (SAEs); discontinuations due to TEAEs; drug interruptions, drug delays and dose reductions due to TEAEs; and TEAE-related mortality (CS Table 12; CS Appendix Table 17). Treatment exposure is summarised in CS Table 11 for the phase I study, phase II study, and integrated analysis; and in CS Appendix Table 16 for the pool 1 and pool 2 analyses.

Immune-related adverse events and potential immunogenicity are important considerations for PD-1 inhibitors,[6] but the CS provides only a brief narrative summary of the total frequency of immune related adverse events (CS section B.2.10.2). Furthermore, immune-related adverse events are missing from the company's list of those adverse events that were included in their economic analysis (CS Table 25). Where necessary we have sourced information on immune-related adverse events from the interim safety summary, which provides more detail[6] (implications for the economic analysis are discussed in section 4.3.6 below). We requested clarification from the company via NICE on how the adverse events reported in CS Table 25 were selected, and why there are some differences in event rates compared to CS Table 13. The company explained (clarification question response A21) that CS Table 13 includes the fixed-dose group, whereas CS Table 25 excludes this group (for consistency with the efficacy data used in the model), but they did not explain how the tabulated adverse events were selected.

3.1.5.5 Timing of outcome assessments

The CS reports that response outcomes were assessed at 4, 6, 8, 12 and 16 months after initiation of cemiplimab therapy. Experts consulted by the ERG considered that these are appropriate time points at which to assess responses, with the exception of the 4-week assessment. At 4 weeks it may be difficult to distinguish true progression from "pseudoprogression" (initial tumour swelling as a result of an immune response at the tumour site).

We note that at the data cut-off, the mean treatment exposure for patients receiving cemiplimab monotherapy for advanced CSCC in the integrated analysis was 26 weeks (CS section B.2.10). The interim safety data currently available may therefore not have captured adverse events that may develop after this time. The ERG notes that a risk of immune related myocarditis has been increasingly observed with immune checkpioint inhibitors (e.g.[22-24]) although it is unclear what the optimal follow-up time to detect such adverse events would be.

> **ERG conclusion:** The survival, response, HRQoL and adverse events outcomes presented by the company are appropriate, although it is not fully clear whether the methods of independent review of response outcomes were comparable in the phase I and phase II studies. HRQoL was assessed using the EORTC QLQ-C30 and a mapping algorithm was applied to obtain EQ-5D utility estimates for the economic analysis.

3.1.6 Description and critique of the company's approach to trial statistics

The analyses presented in the CS are based on interim data. The data for advanced CSCC patients in the phase I study[2] and in the phase II study (section B.3.3) are based on a cut-off date of October 2017. In accordance with the statistical analysis plan, the primary analysis for the phase II study was conducted 6 months after the first dose of cemiplimab had been administered in the last patient to be enrolled.[3] [redacted].

3.1.6.1 Statistical analysis strategy

The company's approach for analysing the clinical effectiveness outcomes in the cemiplimab studies involved pooling the phase I and phase II studies together in what they refer to as an "integrated analysis". The company's rationale is that pooling was clinically plausible due to the similarity of the study methodologies and eligibility criteria, and would improve precision in the estimation of efficacy (CS section B.2.3.1.3). The company's and ERG's clinical expert advisors agreed that pooling the studies was appropriate, but we note that there were some differences in the baseline characteristics of patients in the studies (see section 3.1.3 above), the independent review of response outcomes differed between the studies (see section 3.1.5.1 above), and the studies also differed in their length of follow-up. Median follow-up was slightly

longer in the phase I study [redacted] than the phase II study [redacted] (see section 3.3 below) and in both studies was slightly longer in the laCSCC group than the mCSCC group ([redacted]) (clarification question response A4). We also note that exposure to cemiplimab was longer in the phase I study (mean [redacted] weeks) than in the phase II study (mean [redacted] weeks) and the integrated analysis (mean [redacted] weeks) (CS Table 11). A trade-off of pooling the studies is that whilst the sample size, and hence precision, is increased, the clinical heterogeneity is also increased. We do not consider this to be a major problem, however, as the company has presented the results from the phase I and phase II studies separately alongside the results of the integrated analysis for comparison (see section 3.3 below). As explained above (section 2.1), patients' mCSCC/laCSCC classification differed between the phase I and phase II studies and this was standardised by the company to enable the mCSCC and laCSCC groups to be compared and pooled across the studies.

The company has also pooled together patients with laCSCC and mCSCC in both the phase I and phase II studies and these form the overall "advanced CSCC" population upon which most of the analyses presented in the CS are based. Clinical experts consulted by the ERG agreed that the company's rationale for pooling these groups is generally reasonable, i.e. their eligibility criteria were similar, both groups have similarly poor prognosis with lack of curative therapy options, cemiplimab would be expected to be effective in both groups, and pooling the groups maximises the available sample size. But we note, as explained in section 3.1.6.2 below, that the company assumes that there are some differences in response rates between laCSCC and mCSCC patients.

An issue that arose when pooling the laCSCC and mCSCC groups is that in the phase II study the efficacy data were limited to patients who had the potential for sufficient follow up. This was defined as patients who had the potential for 9 months of follow up (to ensure that a minimum 6-month duration of response requirement set by the US Food and Drug Administration [FDA] would be met). For this reason, the company excluded from the integrated analysis 32 laCSCC patients in the phase II study who did not complete 9 months of follow up, meaning that the full analysis set for the integrated analysis comprised 108 patients. The ERG requested clarification from the company on how inclusion or exclusion of these 32 patients in the integrated analysis would affect clinical effectiveness outcomes, but the company was unable to provide data on these patients due to inadequate follow-up (clarification question response A13).

3.1.6.2 Sample size and power estimation

Phase I study

CS Table 6 states that sample sizes were determined separately for each cohort: 10 patients with mCSCC and 20 patients with laCSCC were to be enrolled. This was achieved for mCSCC (16 enrolled) but not for laCSCC (10 enrolled) (CS Figure 7). The CS does not discuss the implications for statistical power nor how the reclassification of mCSCC and laCSCC in the phase I study for the integrated analysis would have affected this.

Phase II study

CS Table 6 states that sample sizes were determined separately for the mCSCC and laCSCC groups. According to the interim CSR[1] (page 68), "the aggregate experience of patients enrolled in studies of systemic therapy indicated that a clinically meaningful ORR for an investigational agent would be >15% for patients with metastatic disease or >25% for patients with laCSCC". The interim CSR[1] cites four references to support this assertion (Khansur 1991,[25] Lippman 1992,[26] Nakamura 2013[27] and Shin 2002[28]). However, two of these studies were based on very small sample sizes (7 and 8 patients),[25, 27] whilst the cited study by Shin 2002[28] was on patients with head and neck squamous cell carcinoma, not CSCC. The ERG presumes that the interim CSR[1] citation of Shin 2002[28] should instead have referred to a different study on patients with advanced CSCC, Shin 2002.[29] Nevertheless, it is unclear how the data reported in these four studies[25-27, 29] were analysed to obtain the clinically meaningful ORR thresholds stated in the interim CSR[1] (i.e. >25% for patients with laCSCC or >15% for patients with mCSCC). Furthermore, according to CS Table 6 and the interim CSR,[1] the true ORR were assumed to be ≥44% for laCSCC and ≥34% for mCSCC, but the source of these assumptions is not stated.

The sample size calculations (CS Table 6 and interim CSR[1]) assumed a two-sided significance level of no more than 5%, and the resulting sample sizes were increased by 5% to allow for withdrawals. The laCSCC group aimed to recruit 76 patients (allowing for 4 dropouts) to provide ≥90% power to reject a null hypothesis of ORR=25% if the true ORR was 44%; the nonclinically meaningful ORR of 25% was excluded using the lower limit of 95% CI if the observed ORR was around 36.1%. The mCSCC group aimed to recruit 50 patients (allowing for 3 dropouts) to provide ≥85% power to reject a null hypothesis of ORR=15% if the true ORR was 34%; the nonclinically meaningful ORR of 15% was excluded using the lower limit of 95% CI if the observed ORR was around 28.0% or more (CS Table 6 and interim CSR[1]). The laCSCC group

sample size analysed within the phase II study (n=55 or n=23 after exclusion of inadequate follow-up) did not reach that required for the specified ≥90% statistical power (n=76), but the CS does not comment on this.

Integrated analysis

The CS does not discuss the statistical power of the integrated analysis, but states that all integrated analyses are descriptive and no hypothesis testing was conducted based on integrated data (CS section B.2.4 and interim CSR[5]).

3.1.6.3 Analysis populations

The analysis population reported in the CS for clinical effectiveness outcomes in the integrated analysis is described as the full analysis set (FAS). The FAS includes all laCSCC and mCSCC patients in the phase I and phase II studies who received cemiplimab 3 mg/kg q2w, except for 32 phase I study laCSCC patients who did not complete 9 months of follow up (CS section B.2.3.1.3). The FAS also excludes 23 patients who received fixed-dose cemiplimab (group 3) in the phase II study. The ERG requested clarification from the company on the demographic characteristics and clinical effectiveness outcomes of these 23 fixed-dose patients (clarification question response A10). There are some slight differences between this fixed-dose group compared to the rest of the patients in the phase II study (a higher proportion were male and had ECOG performance score 1; and a lower proportion had prior cancer-related systemic therapy, surgery and radiotherapy (Table 4 and clarification question response A10). The analysis of adverse events was conducted in the safety analysis set, as defined above (section 3.1.5.4).

3.1.6.4 Population subgroups

The NICE scope states that, if evidence allows, people with mCSCC, and people with laCSCC for whom there is no curative local therapy (i.e. those with laCSCC who are not candidates for curative surgery or curative radiotherapy, according to the company's decision problem), will be considered as subgroups. The CS reports response rates, time to response, duration of response, and estimated OS and PFS, separately for mCSCC and laCSCC subgroups, and these are reproduced below in section 3.3.4. The CS does not state whether these subgroup analyses were pre-planned or post-hoc; the interim CSR[5] describes them as "exploratory".

The CS presents forest plots reporting hazard ratios for further dichotomous subgroup comparisons in the integrated analysis (CS Appendix Figures 4-6). These are for: gender; age; race; geographic region; number of prior systemic therapies; ECOG performance status; prior systemic anticancer therapy; metastatic status in the mCSCC group; M-stage; T-stage; tumour location; tumour grade; and prior radiotherapy. Some, but not all, of these subgroups were stated as being pre-planned for the phase II study (CS Table 4), but the CS does not report whether they were pre-planned for the integrated analysis. A key limitation of these dichotomous subgroup analyses is the small size of some of the groups. It is unclear whether the confidence intervals of the hazard ratios in these forest plots were adjusted to control the type I error rate in these multiple comparisons (alpha spending is referred to in CS Table 6, but not in relation to subgroup analyses).

The ERG enquired whether the company could provide updated subgroup analyses that include the 32 laCSCC patients who had been excluded for inadequate follow-up. The company confirmed that this was not feasible as no centrally-reviewed data were available for these patients at the latest data cut-off (clarification question response A13).

3.1.6.5 Statistical tests

Formal hypothesis testing was not performed for the integrated analysis. In the phase I and phase II studies response rates were reported descriptively, with the rejection of the null hypotheses being based on comparing the lower 95% confidence interval of the study ORR against the reference ORR (see 3.1.5.2 above). Standard Kaplan-Meier methods were employed for deriving survival curves and hazard ratios for the survival outcomes (CS Table 6).

3.1.6.6 Missing data

Patient discontinuations are reported for the phase I study in CS Appendix Figure 30 and for the phase II study in CS Appendix Figure 31. The study publication[3] and CSRs stat that results are presented in accordance with the intention-to-treat principle but do not define this, and the CS does not refer to intention-to-treat. However, sample sizes reported alongside the results suggest that results for response and survival outcomes are presented for all patients in the FAS, which excludes 32 patients without 9 months follow-up

Censoring rules for DoR, PFS and OS are reported in CS Table 6 for the phase I and phase II studies. These generally follow standard convention and are appropriate.

3.1.6.7 Analysis reporting

Sample sizes, descriptive statistics, and variance estimates including confidence intervals where appropriate are generally reported clearly and consistently, both for the individual phase I and phase II studies and for the integrated analysis. An exception is that the number of patients who provided HRQoL data at each assessment time is not reported in CS Figures 13 and 14. Overall, the analysis methods reported in the CS and study publication are consistent with those specified in the Statistical Plan for each study.

> **ERG conclusion:** The company's approach to trial statistics is broadly appropriate. There are uncertainties regarding the statistical power calculations within the phase II study, but the integrated analysis was descriptive. Some differences exist between the phase I and phase II study methods but results are reported separately for the individual studies and integrated analysis. Subgroups and missing data were generally analysed appropriately, though not all analyses were pre-specified or adjusted for multiple testing.

3.1.7 Description and critique of the company's approach to the evidence synthesis

3.1.7.1 Studies included in the indirect treatment comparison

No direct head-to-head studies of cemiplimab against chemotherapy or BSC were identified and the company therefore investigated the feasibility of conducting an indirect treatment comparison (ITC). The company's feasibility assessment (as described in section 3.1.2 above) excluded a number of studies which did not match the eligibility criteria. The result of this selection process was that the company concluded that no relevant studies of BSC were available, and only one study of chemotherapy in a relevant advanced CSCC population was eligible. The chemotherapy study, by Jarkowski et al. (2016),[8] was a retrospective chart review conducted in the United States which included 25 patients, of whom only 18 had received relevant platinum-based chemotherapy. The ERG's searches (section 3.1.1) and consultation

with three clinical experts did not identify any further eligible comparator studies, either for chemotherapy or BSC, and we concur with the company that, despite its small size and retrospective design, the Jarkowski study[8] appears to provide the best available comparator data for chemotherapy in the advanced CSCC population. The characteristics of the Jarkowski study[8] are summarised in Table 7.

Table 7 Baseline characteristics of the Jarkowski comparator study

Characteristic	All patients (N=25)	laCSCC (N=19)	mCSCC (N=6)
Age, median (range)	66.4 (2.8)	69.2 (3.0)	57.5 (5.5)
Male, n (%)	18 (72)	13 (68.4)	5 (83.3)
Site of primary tumour, n (%)			
Ear	7 (38.0)	5 (26.3)	2 (33.3)
Leg	2 (8.0)	1 (5.3)	1 (16.7)
Face	3 (12.0)	3 (15.8)	0
Trunk	7 (28.0)	6 (31.6)	1 (16.7)
Nose	1 (4.0)	1 (5.3)	0
Hand	1 (4.0)	1 (5.3)	0
Unknown	2 (8.0)	1 (5.3)	1 (16.7)
Penis	2 (8.0)	1 (5.3)	1 (16.7)
Prior therapy, n (%)			
Capecitabine	2 (8.0)	2 (10.5)	0
Cetuximab	12 (48.0)	9 (47.4)	3 (50.0)
Platinum	18 (72.0)	13 (68.4)	5 (83.3)
Taxane	19 (76.6)	13 (68.4)	6 (100)
Source: Jarkowski et al. (2016)[8] (duplicated in CS Appendix Table 9)			

3.1.7.2 Analysis approach

In the absence of direct head-to-head comparisons of cemiplimab against chemotherapy, the company conducted an ITC to compare the effectiveness of cemiplimab in the pooled phase I and phase II studies (i.e. the integrated analysis) against the effectiveness of chemotherapy in the Jarkowski study. The company employed three ITC approaches. These were a naïve indirect comparison (i.e. not adjusting for differences between the studies in patient selection) and two "unanchored" matching exercises: a simulated treatment comparison (STC) (also referred to as an outcome regression) and a matching adjusted indirect comparison (MAIC). These analyses allow adjustment for population differences between the cemiplimab and chemotherapy studies, which is necessary to minimise the risk of the outcomes being subject to

selection bias. In both methods a statistical model is fitted to the individual patient data (IPD) for the reference study population (i.e. the cemiplimab integrated analysis) based on covariates identified in aggregate data from the target study population (i.e. the Jarkowski chemotherapy study) and the reference study population is adjusted to resemble that of the target study. Thus, the cemiplimab IPD are either reweighted to match mean baseline characteristics of the Jarkowski study (MAIC approach), or predictions are made for cemiplimab patients using the mean characteristics of patients in the Jarkowski study (STC approach).

The ERG agrees that the company's approach to the indirect comparison is appropriate, given that direct head-to-head evidence is lacking and that IPD are available for cemiplimab. However there are considerable limitations to both the MAIC and STC approaches, as follows:

- The matching or adjustment will reduce the effective sample size (ESS) for the reference study.
- Both methods match to the target study population rather than to an appropriate real-world population (so it is important that the Jarkowski study adequately reflects patients who would present for advanced CSCC therapy in the NHS).
- Both methods make a fundamental assumption that all effect modifiers and prognostic factors are accounted for in the covariates used in the MAIC or STC. This is considered 'largely impossible' to meet, leading to an unknown amount of bias in the unanchored estimate.[30]

The company's approach to the ITC is described in detail in CS section B.2.8 and the company has provided the R code used to conduct the analyses (clarification question response A16) The ERG requested IPD from the company but these could not be provided due to data ownership rights (clarification question response A16). As far as the ERG can tell, the code is consistent with the NICE DSU guidance on methods for population-adjusted indirect comparisons,[30] although it is not possible to validate the analysis without the accompanying IPD. The company's MAIC and STC methods are consistent with the NICE Decision Support Unit guidance on methods for population-adjusted indirect comparisons.[30] The NICE DSU guidance does not provide any criteria for choosing between STC or MAIC[30] and we consider it appropriate that the company has explored using both approaches.

3.1.7.3 Identification and analysis of prognostic factors

As mentioned above, a strong assumption in MAIC and STC analyses is that all important prognostic factors have been accounted for.[30] The company conducted a targeted literature review to identify prognostic factors, with a search strategy that sought terms based on prognos* in the title or abstract of references. The review identified 28 studies which are not listed in the CS, but details of these have been provided in clarification question response A9. It is possible that the search could have missed studies examining a correlation between outcomes and baseline characteristics, as correlation coefficients can be indicative of prognosis. However, the company supplemented their search by consulting with 11 clinical experts (details of the consultation process and responses of each expert are provided in clarification question response A8). The prognostic factors identified from the search and expert consultation are reported in CS Appendix Table 8 (interpretation of the table is provided in clarification question response A9). Three further clinical experts asked by the ERG concurred that the company's list of prognostic factors is appropriate, except that the company refers under "tumour location" only to scalp or neck tumours being associated with poor prognosis whereas lip, ear and subungual tumours carry a high prognostic risk.

As shown in Table 7, the information available on the characteristics of the patients in the Jarkowski study[8] is very limited. Of 12 prognostic factors identified by the company in CS Appendix Table 8, only gender, disease stage (i.e. mCSCC or laCSCC), tumour location and previous systemic therapies are reported in the Jarkowski study publication[8] in a suitable format for analysis. Median follow-up in the study was 42.8 months (range 11.5 to 62 months). The relevant patients in the study were the 18 who received platinum-based chemotherapy, and Kaplan-Meier OS and PFS curves are available for this group in the study publication.[8] The company extracted the survival outcomes by digitising the curves, as reported in CS section B.2.9.2.4.

The company compared two models comprising different sets of prognostic factors in the matching, and they used the Akaike information criterion (AIC) to assess model fit. The models are not defined in the CS but the company provided definitions in clarification question response A14:

- a core model matched on disease stage and location, and
- an extended model added gender and prior systemic therapy

The extended model gave a lower AIC but also gave coefficients opposite to the expected direction of effect, and when gender (which was not prognostic) was removed gave similar results to the core model which was preferred. The direction of effect for tumour location in OS and PFS analyses was contrary to expectation, with a lower HR for head and neck tumours (and therefore better prognosis for these tumours), which the Company attributed to the low sample size. This pattern was observed for both the core and extended models. Hence, ultimately only tumour stage and location were matched between studies. It was not possible to match on any of the other prognostic factors such as age, immune status, tumour differentiation grade, tumour depth, performance status, and previous radiotherapy, due to lack of data.

The CS does not report whether the company attempted to estimate the extent of systematic error due to unaccounted for covariates using out-of-sample or in-sample methods as proposed in the NICE DSU guidance on methods for population-adjusted indirect comparisons.[30] However, we agree with a comment by the company (in their Factual Inaccuracy Check response) that this would not have been feasible given the lack of available data.

3.1.7.4 Role of the ITC in informing the economic model

The company preferred the results of the naïve comparison and STC for informing their economic model. The naïve comparison was selected as being the most conservative analysis rather than being methodologically appropriate. Naïve comparisons are not recommended and should be viewed with caution due to potential selection bias. The company's argument for choosing the STC over the MAIC is that reweighting the cemiplimab patients in the MAIC lowered the expected sample size (ESS) on an already small study (n=108). There is no guidance on a threshold for ESS, indeed studies have been published using a lower ESS (e.g. Nash et al. 2018[31]), but a low ESS is indicative both of limited overlap between populations (in which the majority of patients are dropped following matching) and a relatively small sample size. The company reports that six laCSCC patients accounted for the majority of the ESS (CS section B.2.9.3.1 and clarification question response A12). We believe this is a reasonable justification for the company's preference for selecting the STC over the MAIC.

3.1.7.5 Summary of the ITC approach

The ERG's critique of the ITC is summarised in Table 8 below. Overall we agree that the company's approach to the ITC is appropriate for an analysis attempt given the lack of available data, and the analysis is generally well reported and consistent with NICE DSU guidance.

However, the data shortage is serious and imparts major uncertainty to the results obtained from the analyses. In summary:

- The comparator study included only 18 relevant patients; these are unlikely to be representative of the full spectrum of patients eligible for analysis. It is unclear how relevant the comparator study is for patients presenting for advanced CSCC therapy in the NHS.
- The comparator study was retrospective and so might be biased.
- The ITC could only include two of 12 prognostic covariates identified as potentially important by the company and experts.
- MAIC methods of ITC further reduce the already small effective sample size.
- Naive comparisons are inadvisable as effectiveness outcomes are highly likely to be confounded with population differences between the studies.
- The studies had relatively short duration; data immaturity reflects that the studies are currently ongoing.
- The uncertainty arising from the aforementioned issues is not captured in the ITC statistical variance measures such as 95% confidence intervals. There is a risk therefore that the outcomes and effectiveness estimates may appear to be more precise than is the case in reality.

Table 8: ERG's appraisal of the indirect treatment comparison (ITC) approach

Checklist question	ERG response
Does the CS present an ITC?	Yes, two basic two-study unanchored matched comparisons and a naive comparison
Are the ITC results used to support the evidence for the clinical effectiveness of the intervention	Implicitly, but acknowledged that interpretation is hindered by uncertainty
Are the ITC results used to support the evidence for the cost-effectiveness of the intervention	Yes: naive comparison with STC as a scenario
Homogeneity	
1. Is homogeneity considered?	No, but heterogeneity is acknowledged narratively

	2. Are the studies homogenous in terms of patient characteristics and study design?	Uncertain due to limited data reported
	3. Is the method used to determine the presence of statistical heterogeneity adequate? (e.g. Chi-squared test, I-squared statistic)	Heterogeneity was not assessed statistically
	4. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across studies in each set involved in the indirect comparison investigated by an adequate method? (e.g. subgroup analysis, sensitivity analysis, meta-regression)	No, sample sizes are already very small
Similarity		
	1. Is the assumption of similarity stated?	No
	2. Have they justified their assumption?	Not applicable
Consistency		Not applicable

ERG conclusion: The statistical approaches for the indirect comparisons have strong limitations, including that only one very small single-arm comparator study was available which was at high risk of bias; the studies could not be matched for the majority of important prognostic variables; and data are immature. The company and ERG agree that results of these analyses are therefore highly uncertain.

3.2 Summary statement of the company's approach

The ERG's assessment of the company's approach to the clinical effectiveness evidence synthesis is summarised in Table 9 below. The company's approach for identifying and selecting evidence is consistent with their decision problem. Overall the company has followed good practice for minimising the risk of bias in the review process, by conducting extensive searches for studies and by employing two independent reviewers to make eligibility decisions. As noted above (section 3.1.4) the company assessed the "quality" of studies using the Newcastle-Ottawa scale, but they do not discuss study validity (i.e. risk of bias). The main limitations of the cemiplimab and chemotherapy studies are that they were single-arm and had relatively short follow-up, whilst the main limitations of the chemotherapy study are that it was single-arm and retrospective.

Table 9 Quality assessment (CRD criteria) of the CS review of clinical effectiveness

CRD Quality Item	ERG comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Partly. Inclusion and exclusion criteria are clearly tabulated (CS Appendix Table 7). However, further exclusions in the "feasibility assessment" are reported narratively post-hoc,

	such as for specific interventions and for studies without Kaplan-Meiersurvival curves. The post-hoc refinement of eligibility criteria during the feasibility assessment could have introduced selection bias (although the ERG and clinical expert advisors did not identify any key studies that had been missed).
2. Is there evidence of a substantial effort to search for all relevant research, i.e. all studies have been identified?	Yes. The company's searches were fit for purpose. ERG searches, consultation with clinical experts, and enquiry to the National Disease Registration Service did not identify any further studies or relevant comparator datasets.
3. Is the validity of included studies adequately assessed?	Partly. The company used the Newcastle-Ottawa scale to assess "quality" of the cemiplimab studies and the Jarkowski chemotherapy comparator study but does not discuss how this relates to validity (i.e. risk of bias). The ERG does not fully agree with the company's assessments (Appendix 2).
4. Is sufficient detail of the individual studies presented?	Yes. Extensive details of the cemiplimab studies are provided. All available details of the comparator study (which are very limited) are also reported.
5. Are the primary studies summarised appropriately?	Yes, all studies analysed are reported in sufficient detail.

3.3 Summary of the submitted evidence

Median follow-up was [redacted]) in the phase I study, [redacted] in the phase II study, and 8.92 months (range 0.8-15.9 months) for the integrated analysis (clarification question response A4).

3.3.1 Response rates

Response rate outcomes are summarised in Table 10 and Table 11. ORR was the primary outcome of the phase II study (but not the phase I study). The ORR for the integrated analysis was [redacted]. The median duration of response, DOR, [redacted] in either of the studies or the integrated analysis, with response durations ranging from [redacted] and [redacted]. DOR was at least 6 months in [redacted] of participants. Mean time to response, TTR, was [redacted] in the integrated analysis, with [redacted] of patients experiencing this in less than 2 months [redacted]. Response data are not used in the company's economic model.

Table 10 Response outcomes, full analysis set

Outcome	Integrated analysis (N=108)	Phase I study (N=26)	Phase II study (N=82)
ORR, n (%)	[redacted]	13 (50.0)	[redacted]

Outcome	Integrated analysis (N=108)	Phase I study (N=26)	Phase II study (N=82)
[95% CI]	[redacted]	[29.9, 70.1]	[redacted]
Best overall response, n (%)			
Complete response - CR	[redacted]	0	[redacted]
Partial response - PR	[redacted]	13 (50.0)	[redacted]
Stable disease - SD	[redacted]	[redacted]	[redacted]
Non-CR/Non-PD	[redacted]	[redacted]	[redacted]
Progressive disease - PD	[redacted]	[redacted]	[redacted]
Not evaluable [a]	[redacted]	3 (11.5)	[redacted]
Disease control rate – DCR, n (%) [95% CI]	[redacted]	20 (76.9) [56.4, 91.0]	[redacted]
Durable DCR [95% CI]	[redacted]	17 (65.4) [44.3, 82.8]	[redacted]
Mean TTR, months (SD)	[redacted]	[redacted]	[redacted]
<2 months	[redacted]	[redacted]	[redacted]
2 to 4 months	[redacted]	[redacted]	[redacted]
4 to 6 months	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]

Source: CS Table 7. DCR = CR + PR + SD + Non-CR + Non-PD; TTR: time to response.
[a] Patients without a post baseline assessment.

Table 11 Duration of response outcomes, full analysis set

Outcome	Integrated analysis (N=51)[a]	Phase I Study (N=13)	Phase II study (N=38)
Kaplan-Meier estimate of DOR			
Events[b], n (%)	[redacted]	[redacted]	[redacted]
Median months (95% CI)	[redacted]	NR (NE, NE)	[redacted]
Observed DOR, n (%)			
N (min, max)	[redacted]	[redacted]	[redacted]
≥4 months	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]
≥8 months	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]

Source: CS Table 8. NE: not evaluable; NR: not reached.
[a] Stated N=108 in CS Table 8; ERG presumes this is an error.
[b] Events include progressive disease or deaths; + ongoing at last assessment

ERG conclusion: The objective response rate in the integrated analysis was favourable, although median follow-up was only 8.9 months. Most responses

were partial responses. Median duration of response was not reached. These response outcomes do not inform the company's economic analysis.

3.3.2 Survival

At a median follow-up of [redacted], median overall survival, OS, was [redacted] in either study or the integrated analysis (Table 12). Estimated 12-month survival was [redacted] in the integrated analysis and was similar across studies.

Median progression-free survival, PFS, was [redacted]. The estimated 12-month PFS was [redacted] in the integrated analysis [redacted] (Table 12).

OS and PFS data from the integrated analysis are used in the company's economic model.

Table 12 Survival outcomes, full analysis set

Outcome	Integrated analysis (N=108)	Phase I study (N=26)	Phase II study (N=82)
Median OS, months (95% CI)	[redacted]	NR ([redacted])	NR (NE, NE)
Estimated event-free probability, % (95% CI)			
12 months	[redacted]	[redacted]	[redacted]
16 months	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]
Estimated event-free probability, % (95% CI)			
12 months	[redacted]	[redacted]	[redacted]
16 months	[redacted]	[redacted]	[redacted]

Source: CS Table 9. NE, not evaluable; NR: not reached.

ERG conclusion: Due to the relatively short follow-up, median OS and median PFS were not reached. Nevertheless, these survival outcomes inform the company's economic analysis (section 4.3.4).

3.3.3 Health related quality of life

HRQoL data were not collected in the phase I study. In the phase II study, the CS states that [redacted] (the clinical relevance of EORTC QLQ-30 scores is

considered above in section 3.1.5.3). Data from the EORTC QLQ-C30 scores in the phase II study inform the company's economic model: they were converted to EQ-5D utility values for the model in a mapping exercise (section 4.3.6).

ERG conclusion: The EORTC QLQ-C30 scale indicated [redacted] while patients in the phase II study were receiving cemiplimab. However, the clinical significance of this is uncertain.

3.3.4 Sub-group analysis results

The NICE scope lists mCSCC and laCSCC subgroups for consideration. The CS presents data for these subgroups in CS Figure 8 and CS Appendix L. Median follow-up for the mCSCC group was [redacted] in the phase I study and [redacted] in the phase II study. For the laCSCC group, median follow-up was [redacted] in the phase I study and [redacted] in the phase II study (clarification question response A4). Response outcomes for the mCSCC and laCSCC groups are shown in Table 13 and Table 14 below.

In the integrated analysis for the mCSCC group, an ORR of [redacted] was found [redacted] phase II study 47.5% [95% CI 34.3 to 60.9]). For the laCSCC group, an ORR of [redacted] was found [redacted] study [redacted] (Table 13).

Table 13 Response outcomes by disease subgroups

Outcome	Integrated analysis (N=108)		Phase I study (N=26)		Phase II study (N=82)	
	mCSCC (n=75)	laCSCC (n=33)	mCSCC (n=16)	laCSCC (n=10)	mCSCC (n=59)	laCSCC (n=23)
ORR, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	28 (47.5) [34.3, 60.9]	[redacted]
Best overall response, n (%)						
CR	[redacted]	[redacted]	[redacted]	[redacted]	4 (6.8)	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	24 (40.7)	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	9 (15.3)	[redacted]
Non-CR/Non-PD	[redacted]	[redacted]	[redacted]	[redacted]	4 (6.8)	[redacted]

PD	[redacted]	[redacted]	[redacted]	[redacted]	11 (18.6)	[redacted]
NE	[redacted]	[redacted]	[redacted]	[redacted]	7 (11.9)	[redacted]
DCR, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	41 (69.5) [56.1, 80.8]	[redacted]
Durable DCR, n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	36 (61.0) [47.4, 73.5]	[redacted]
Mean TTR, months (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<2 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2 to 4 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4 to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: CS Appendix Table 45. For abbreviations and definition of DCR see Table 10 above.						

Although the interim CSR for the phase II study suggests that response rates differ between mCSCC and laCSCC groups (see section 3.1.6.2), it is difficult to get a clear sense of this from the cemiplimab studies, since the differences in ORR between the mCSCC and laCSCC subgroups were not consistent across the phase I and phase II studies (Table 13). There was a tendency, however, for the frequency of partial responses to be higher and the frequency of progressive disease to be lower in the laCSCC groups, as well as the laCSCC groups having a higher disease control rate but longer TTR (Table 13). Given the small sample sizes and immaturity of the data, and the fact that median follow-up was slightly longer in the laCSCC group, it is unclear how robust these differences between the mCSCC and laCSCC groups are.

Median DOR [redacted] in either subgroup, with response durations in the integrated analysis ranging from [redacted] in mCSCC, and [redacted] in laCSCC (Table 14).

Table 14 Duration of response outcomes by disease subgroups

Outcome	**Integrated analysis (N=51)**		**Phase I study (N=13)**		**Phase II study (N=38)**	
	mCSCC (n=35)	**laCSCC (n=16)**	**mCSCC (n=7)**	**laCSCC (n=6)**	**mCSCC (n=28)**	**laCSCC (n=10)**
Kaplan-Meier estimate of DOR						

Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed DOR, n (%)						
N (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥8 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: CS Appendix Table 46. NE, not evaluable; NR: not reached; + ongoing at last assessment.						

Median OS and PFS [redacted] in the mCSCC and laCSCC groups (Table 15). In the integrated analysis, estimated 12 month OS was [redacted] in the mCSCC group and [redacted] in the laCSCC group, with a similar pattern of OS being higher in the laCSCC group than the mCSCC group in both the individual studies. Estimated 12 month PFS was [redacted] for the mCSCC group and [redacted] for the laCSCC group.

Table 15 Survival outcomes by disease subgroups

Outcome	Integrated analysis (N=108)		Phase I study (N=26)		Phase II study (N=82)	
	mCSCC (n=75)	laCSCC (n=33)	mCSCC (n=16)	laCSCC (n=10)	mCSCC (n=59)	laCSCC (n=23)
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated event-free probability, % (95% CI)						
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated event-free probability, % (95% CI)						
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

16 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: CS Appendix Tables 47 and 48. NE, not evaluable; NR: not reached						

As noted above (section 3.1.6.4), the company reports further subgroup analyses for a range of prognostic and demographic factors and these are presented in forest plots for the integrated analysis of OS, PFS and ORR (CS Appendix Figures 4 to 6). As these additional subgroups (listed in section 3.1.6.4) are not specified in the NICE scope and are generally based on small sample sizes we have not reproduced them here. Overall (as stated in CS Appendix E), subgroup analysis results were generally in line with expectations, [redacted] However, contrary to expectations, [redacted] (i.e. [redacted] tumours[32]) [redacted] (i.e. [redacted] tumours[32]). The subgroup results should be viewed with caution due to small sample sizes and absence of interaction tests.

> **ERG conclusion**: There were some differences in the frequencies of partial responses, progressive disease, disease control rate, and the time to response between the mCSCC and laCSCC groups. These, apart from TTR, generally favoured the laCSCC groups but it is unclear how robust they are, given the small sample sizes and immature data. Differences in ORR were not consistent between the mCSCC and laCSCC groups across the phase I and phase II studies. Median OS and PFS had not been reached in the mCSCC and laCSCC groups.

3.3.5 Indirect comparison results

At a median follow-up of 42.8 months (range 11.5 to 62 months) the results from the Jarkowski comparator study platinum chemotherapy group (n=18) were: OS 15.1 months; PFS 9.8 months; and ORR 56%.

[redacted] (Table 16). [redacted].

Table 16 Indirect comparison results

Outcome	Analysis method		
	Naïve	STC	MAIC
OS, HR (95% CI)	[redacted]	[redacted]	[redacted]
PFS, HR (95% CI)	[redacted]	[redacted]	[redacted]
ORR, OR (95% CI)	[redacted]	[redacted]	[redacted]

Source: CS Figures 16, 18 and 20. HR: hazard ratio; MAIC, matching-adjusted indirect comparison; OR: odds ratio; Naïve: unadjusted indirect comparison; STC: simulated treatment comparison.

ERG conclusion: Results of the indirect treatment comparisons suggest that cemiplimab improved OS and PFS when compared to platinum-based chemotherapy. However, both the company and ERG agree that due to limitations of the analyses these results are highly uncertain, precluding any meaningful conclusions.

3.3.6 Adverse events

The CS presents key adverse event data from the two pivotal studies (phase I, n=26; phase II n=137) and the integrated analysis set (n=163), described as the safety analysis set. This included all CSCC patients who received at least 1 dose of cemiplimab monotherapy, including those in the 350mg fixed-dose group of the phase II study. The median follow-up for this safety set is unclear. In addition, CS Appendices F1 and F2 present summary adverse event data for the locally advanced and metastatic subgroups and the wider cemiplimab treated population in the phase I study respectively. The ERG has checked these data with sources and there are no issues of consequence in terms of their accuracy (a few minor differences in the totals for each system class but these would likely have a conservative effect). Here we summarise the key adverse event data.

3.3.6.1 Overall rates of adverse events

Table 17 summarises the overall rates of adverse events. In the integrated analysis, [redacted] experienced a treatment emergent adverse event (TEAE); [redacted] with at least one Grade ≥3. [redacted] were the most commonly reported TEAEs over all grades (for full data see CS Table 13). TEAEs considered by the investigator to be related to cemiplimab were experienced by [redacted], most frequently [redacted].[6]

Table 17 Overview of adverse events, safety analysis set

Event	Integrated analysis (N=163)	Phase I Study (N=26)	Phase II study (N=137)
Any TEAE, %	[redacted]	[redacted]	[redacted]
Grade 3–5 TEAE, %	[redacted]	[redacted]	[redacted]
Any SAE, %	[redacted]	[redacted]	[redacted]
Discontinuations due to TEAEs, %	[redacted]	[redacted]	[redacted]
TEAE leading to drug interruption/delay, %	[redacted]	[redacted]	[redacted]
TEAE leading to a dose reduction, %	[redacted]	[redacted]	[redacted]
TEAE leading to death, %	[redacted]	[redacted]	[redacted]
Source: CS Table 12. SAE: serious adverse event; TEAE: treatment-emergent adverse event.			

A total of [redacted] patients discontinued the study drug due to TEAEs. Deaths occurred in [redacted]). The most common primary cause of death was reported to be [redacted].[6] TEAEs leading to death occurred in [redacted].[6]

The proportion with at least one serious adverse event (SAE) was [redacted]. The most common SAEs were [redacted][6] The CS states that [redacted] (no details of these management approaches are reported in the safety analysis summary[6]).

TEAEs resulting in drug interruption or delay were experienced in [redacted] of patients. The most common reason was because of infusion related reactions (IRR) ([redacted]) followed by pneumonia, cellulitis, diarrhoea, and fatigue ([redacted] each).[6]

The CS presents summary adverse events for the mCSCC and laCSCC groups from the phase I and phase II studies in Appendix F.1. In the laCSCC groups (n=65) between [redacted] had any TEAE and between [redacted] a Grade 3-5 event (CS Appendix Table 17). SAEs were experienced in [redacted] and TEAE leading to death occurred in [redacted]. In the mCSCC groups (n=98) [redacted] had any TEAE, [redacted] a Grade 3-5 event and [redacted] a SAE. [redacted] people had a TEAE that led to death ([redacted]).

3.3.6.2 Specific treatment-emergent adverse events

In the integrated analysis, [redacted] of participants experienced as least one grade ≥3 TEAE (Table 17). The most frequent classes of grade ≥3 TEAEs are summarised in Table 18. Grade ≥3 infections and infestations affected [redacted] of patients, the most frequent being cellulitis ([redacted]), sepsis ([redacted]), urinary tract infection and pneumonia ([redacted] each) (CS Table 13). Grade ≥3 metabolic and nutrition disorders affected [redacted] of patients, most frequently hypercalcaemia ([redacted]) and hyponatraemia ([redacted]) (CS Table 13). Immune-related adverse events (irAEs), [redacted] (referred to as 'identified irAEs'),[6] occurred in [redacted], with [redacted] having a Grade ≥3 irAE. The respective frequencies with 'potential irAEs' (the broadest assessment of irAEs) were [redacted] and [redacted] respectively. The most frequent 'identified' irAEs at Grade ≥3 were [redacted]. The CS does not report the frequency of infusion-related reactions (IRR) in the integrated analysis, but the safety analysis summary[6] states that there were no Grade ≥3 IRR.

Table 18 Most frequent TEAE types of Grade ≥3, safety analysis set

Event [a]	Integrated analysis (N=163)	Phase I Study (N=26)	Phase II study (N=137)
Infections and infestations, %	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders, %	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions, %	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders, %	[redacted]	[redacted]	[redacted]
Vascular disorders, %	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders, %	[redacted]	[redacted]	[redacted]
Investigations, %	[redacted]	[redacted]	[redacted]

Source: CS Table 13.
[a] Events with frequency >5% in either study or the integrated analysis, ordered by frequency of occurrence in the integrated analysis

3.3.6.3 Adverse events in wider cemiplimab-treated cohorts

As well as adverse events for all CSCC patients who received cemiplimab as part of the phase I and phase II studies of relevance to the decision problem, the CS presents a summary of

adverse events encompassing these data together with data from two wider cohorts (CS Appendix F.2):

- "Pool 2": cemiplimab monotherapy cohorts in the phase I study except hepatocellular carcinoma ([redacted]), plus all phase II study groups (i.e. both weight-based and fixed dose groups combined) (n=240, including 77 [32%] with non-CSCC solid tumours).
- "Pool 3": all phase I study cemiplimab monotherapy and combination therapy cohorts, including 26 hepatocellular carcinoma patients, plus all phase II study groups (i.e. weight-based and fixed dose groups combined) (n=534).

In addition to advanced CSCC, the Pool 2 and Pool 3 analyses included patients in the phase I study with a diverse range of other advanced solid tumours (31 tumour types are listed in Table 7 of the interim safety summary[6]). We note that [redacted] of the patients ([redacted] 23 in the phase II study) had received a cemiplimab dose other than 3 mg/kg q2w in these pooled analyses. The interim safety analysis summary acknowledges that while Pool 3 is the largest safety cohort it is a heterogeneous group that includes patients receiving concomitant chemotherapy and radiotherapy; it is provided as supporting information in relation to deaths, immune-related adverse events and immunogenicity,[6] and does not inform the company's economic analysis. Note that these are nested safety cohorts, as all patients in the integrated analysis were included within Pool 2, and all patients in Pool 2 were included within Pool 3.[6]

Exposure to cemiplimab is summarised in CS section B.2.10.1 for the integrated analysis and in CS Appendix F and the safety analysis summary[6] for Pool 2 and Pool 3. At the latest reported data cut-off, mean (SD) exposure to ≥1 dose of cemiplimab was [redacted] weeks in the integrated analysis, [redacted] weeks in Pool 2 and [redacted] weeks in Pool 3. Corresponding median exposure durations were [redacted] in Pool 2, and [redacted] in Pool 3.

Below we provide an overview of adverse events (Table 19) and list the most frequent types of TEAEs (Table 20) in these safety cohorts. Overall, the types and frequencies of adverse events were broadly similar between the largest safety cohort, Pool 3, which included cemiplimab combination therapies, and Pool 2, which was limited to cemiplimab monotherapy (with differing dose regimens). Despite these large safety cohorts including patients with non-CSCC solid tumours, the overall types and frequencies of adverse events are broadly similar to those seen

in the integrated analysis for advanced CSCC. Where differences exist between the Pool 3 and integrated analysis these were usually within 5 percentage points (e.g. Grade 3/4/5 gastrointestinal disorders [redacted] in Pool 3 versus [redacted] in the integrated analysis; metabolic and nutrition disorders [redacted] versus [redacted] respectively; and infections and infestations [redacted] versus [redacted] respectively.

Table 19 Overview of adverse events in wider cemiplimab cohorts

Event	Integrated analysis, advanced CSCC (N=163)	Pool 2 (cemiplimab monotherapy, mixed tumours) (N=240)	Pool 3 (cemiplimab mono- and combination therapy, mixed tumours) (N=534)
Any TEAE, %	[redacted]	[redacted]	[redacted]
Grade 3–5, %	[redacted]	[redacted]	[redacted]
Any SAE, %	[redacted]	[redacted]	[redacted]
Discontinuations due to TEAEs, %	[redacted]	[redacted]	[redacted]
TEAE leading to drug interruption/delay, %	[redacted]	[redacted]	[redacted]
TEAE leading to a dose reduction, %	[redacted]	[redacted]	[redacted]
TEAE leading to death, %	[redacted]	[redacted]	[redacted]
Source: CS Appendix Table 19. SAE, serious adverse event; TEAE, treatment-emergent adverse event.			

According to the safety analysis summary,[6] the rate of irAE in Pool 3 was [redacted] as compared to [redacted] in the integrated analysis (as described above).

As noted above, the CS does not report the rate of infusion-related reactions (IRR) for the integrated analysis, but the safety analysis summary[6] reports that in Pool 3 the frequency of IRR was [redacted], all of which except [redacted] were ≤ Grade 3.

Table 20 Most frequent TEAE types (≥1% grade 3/4/5) in wider cemiplimab cohorts

Event	Pool 2 (cemiplimab monotherapy) (N=240)	Pool 3 (cemiplimab mono- and combination therapy) (N=534)
Gastrointestinal disorders, %	[redacted]	[redacted]
General disorders and administration site conditions, %	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders, %	[redacted]	[redacted]
Metabolism and nutrition disorders, %	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders, %	[redacted]	[redacted]

Event	Pool 2 (cemiplimab monotherapy) (N=240)	Pool 3 (cemiplimab mono- and combination therapy) (N=534)
Skin and subcutaneous tissue disorders, %	[redacted]	[redacted]
Infections and infestations, %	[redacted]	[redacted]
Nervous system disorders, %	[redacted]	[redacted]
Investigations, %	[redacted]	[redacted]
Blood and lymphatic system disorders, %	[redacted]	[redacted]
Psychiatric disorders, %	[redacted]	[redacted]
Injury, poisoning and procedural complications, %	[redacted]	[redacted]
Vascular disorders, %	[redacted]	[redacted]
Renal and urinary disorders, %	[redacted]	[redacted]
Endocrine disorders, %	[redacted]	[redacted]
Cardiac disorders, %	[redacted]	[redacted]
Hepatobiliary disorders, %	[redacted]	[redacted]
Source: CS Appendix Table 20		

3.3.6.4 Comparison of adverse events for other immune checkpoint inhibitors

No adverse event data are available in comparable CSCC populations. The CS cites a study by Tsiatas et al. (2016)[33] when stating that cemiplimab has demonstrated a predictable and manageable safety profile consistent with that seen with other PD-1 inhibitors. The ERG has checked the Tsiatas et al. publication[33] and we note that there are no data in which to compare the toxicity of cemiplimab with other PD-1 inhibitors. We have identified a recent systematic review and network meta-analysis of the safety of immune checkpoint inhibitors in cancer (of any type) by Xu et al. (2018)[34] which may provide some context to the safety profile of cemiplimab. The pooled incidence of grade 3 or 4 treatment related adverse events were: 14.1% and 19.8% respectively for the PD-1 inhibitors nivolumab and pembrolizumab; and 15.1% for the PD-L1 inhibitor atezolizumab. This compares with [redacted] having at least one Grade ≥3 treatment related adverse event (i.e. irAE) in the safety analysis set of the cemiplimab studies. We note that irAE reported in the cemiplimab studies do not include infusion related reactions, of which there were [redacted] in the Pool 3 safety analysis ([redacted] in the integrated analysis). An important limitation of these comparisons is that the studies included in the meta-analysis by Xu et al.[34] were heterogeneous in terms of the cancer types and length of follow-up, and Xu et al.[34] did not report the age of participants included in their analysis or the comorbidities experienced by patients. It is therefore unclear how comparable these rates of adverse events would be to a population with advanced CSCC.

The CS states that, overall, the SAEs reported for cemiplimab are typical for a population of this age with advanced cancer but no references are provided (CS section A.6.5). Two of four clinical experts advising the ERG agreed that this is a reasonable conclusion. A further expert suggested that safety data for avelumab in Merkel cell carcinoma could be relevant for comparison, as the presenting population would have a similar age profile and prognosis. However, although adverse events data have been reported for avelumab in Merkel cell cancer these are unavailable for comparison (the data are redacted in the relevant NICE Technology Appraisal, TA517[35]).

> **ERG conclusion**: The CS presents an overview of the safety profile of cemiplimab from the phase I and phase II studies, both for patients receiving monotherapy for advanced CSCC and for wider cohorts receiving cemiplimab monotherapy and combination therapy for other solid tumours. No directly comparable adverse events data are available for other PD-1 or PD-L1 inhibitors in advanced CSCC. Some comparisons can be made with PD-1 and PD-L1 inhibitors used for other cancers and whilst these do not raise any major safety concerns, it is unclear how generalisable these comparisons are to people who have advanced CSCC. Given the immature data available, the longer-term safety profile of cemiplimab is uncertain.

3.4 Conclusions of clinical effectiveness

Decision problem and scope: The company's decision problem is consistent with the NICE scope, although no evidence was identified for the BSC comparator. The dose regimen in the CS differs from that of the company's anticipated marketing authorisation. The company conducted PK modelling do demonstrate the equivalence of the two regimens but this approach has some uncertainties.

Clinical effectiveness searches and study selection: The ERG and clinical expert advisors believe the company has included all available relevant cemiplimab and comparator studies. Given the lack of evidence for BSC, studies of chemotherapy and EGFR inhibitors are used as proxies for BSC in the company's economic analysis.

Cemiplimab effectiveness evidence: The effectiveness evidence for cemiplimab is from two non-comparative phase I and phase II ongoing studies with small sample sizes (total N=108) and immature data. Clinical experts agreed that pooling these studies in an 'integrated' analysis was appropriate. There is some heterogeneity in the populations in the two studies, mainly concerning the extent of prior cancer-related therapy, and there were differences in cemiplimab exposure and follow-up, but the importance of these differences is uncertain due to the small sample sizes. Clinical experts also agreed that pooling together the laCSCC and mCSCC groups in the integrated analysis was appropriate. There were some differences in response outcomes between these groups but it is unclear how robust the differences are, given the small sample sizes and immature data. Median OS and PFS had not been reached in the mCSCC and laCSCC groups, although these outcomes inform the economic analysis.

Cemiplimab safety evidence: The safety analysis set did not identify any unexpected safety concerns but is based on short follow-up. The longer-term safety of cemiplimab is uncertain. No comparative safety data are available for other PD-1 or PD-L1 inhibitors in the advanced CSCC population. Comparisons with the safety of these immune checkpoint inhibitors in other cancers can be made but populations are heterogeneous and generalisability is uncertain.

Indirect treatment comparison: The MAIC, STC and naïve analysis approaches for the indirect comparisons have strong limitations, including that only one very small (N=18) single-arm chemotherapy comparator study was available which was retrospective and at high risk of bias; the studies could not be matched for the majority of important prognostic variables; and data are immature. The company and ERG agree that results of these analyses are highly uncertain. Nevertheless, the naïve and STC analyses of OS and PFS inform the economic analysis (the naïve analysis gave the most conservative results).

Overall conclusion: The small size of the studies, immaturity of data, lack of comparative studies, and limited reporting of prognostic variables in the studies means that although the evidence for the clinical effectiveness of cemiplimab appears

promising, it is highly uncertain. Given that the limitations are inherent in the evidence base it is very difficult for the ERG to reduce this uncertainty. It should be borne in mind that whilst some of the statistical analyses conducted both by the company and the ERG provide estimates of precision (e.g. in credible intervals and confidence intervals), these do not fully capture the uncertainty. The ERG has attempted to illustrate the most likely ranges of outcomes within this uncertainty when assessing the company's economic analysis (section 4 below) but the only definitive way to reduce the uncertainty would be to collect further data.

4 COST EFFECTIVENESS

4.1 Overview of the company's economic evaluation

The company's submission to NICE includes:

iii) a review of published economic evaluations of treatments for people with advanced CSCC (CS section B.3.1 and CS Appendix G).

iv) a report of an economic evaluation undertaken for the NICE STA process (CS sections B.3.2 to 3.2.10. The cost effectiveness of cemiplimab is compared with chemotherapy and BSC for people with advanced CSCC who are not candidates for curative surgery or curative radiotherapy.

4.2 Company's review of published economic evaluations

The company's search strategy for cost-effectiveness studies was appropriate. The company performed their initial search in October 2017 and updated it in September 2018. We performed a simple unstructured search in Google Scholar to identify any more recent publications but did not identify any further directly relevant studies.

CS Table 15 summarises the review inclusion and exclusion criteria. The review included economic evaluations and cost studies of drug treatments for people with CSCC and either locally advanced disease not suitable for surgery, or nodal or distant metastases. Studies relating to any other skin cancers (including basal cell carcinoma, melanoma or head and neck squamous cell carcinoma) or for patients who were candidates for surgery or radiation were excluded.

The results of the search are summarised in a PRISMA diagram in CS Figure 21. Of 459 references screened, the company identified five studies for full-text screening, of which four were excluded. The single study that met the inclusion criteria was a cost analysis conducted in South Africa for patients with skin cancer. Whilst the study included CSCC patients with nodal involvement, it did not separate patients with CSCC from those with basal cell carcinoma. Therefore, the company stated that this study was not applicable for the purpose of this appraisal.

ERG conclusion: The company conducted a comprehensive search for economic evaluations related to the decision problem, with appropriate eligibility criteria and the

findings are well-documented. We agree with the conclusion that no relevant economic evaluations were identified.

The company's search included NICE and other selected HTA agency websites but did not identify any technology appraisals for the relevant population. The ERG considered whether NICE guidance for other skin cancers may contain information or accepted assumptions relevant to the current economic evaluation. In particular, we were interested in alternative sources for comparison of company estimates of utilities, resource use, adverse event incidence and the duration of treatment effects. Our clinical advisors suggested that health-related quality of life and use of supportive care is likely to be quite different for people with head and neck squamous cell carcinoma (HNSCC) or melanomas than for those with CSCC, but that Merkel cell carcinoma and basal cell carcinoma are more comparable. Given the sparsity of the evidence base on cemiplimab, evidence and accepted assumptions about safety and the duration of effects for other PD-1 inhibitors may be informative, although clinically important differences in safety profiles of immune checkpoint inhibitor drugs have been observed.[34]

- For utility and resource use, we compare with information from:
    - Avelumab for metastatic Merkel cell carcinoma: (TA517)[35]
    - Vismodegib for metastatic or locally advanced basal cell carcinoma (TA489)[36]

- For duration of treatment effect and risks of adverse events, we make comparisons with NICE appraisals of nivolumab or pembrolizumab for other advanced skin cancers:
    - Nivolumab for advanced melanoma (TA384)[37]
    - Nivolumab for HNSCC after platinum-based chemotherapy (TA490)[38]
    - Pembrolizumab for advanced melanoma not previously treated with ipilimumab (TA366) [39]

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

The ERG's assessment of whether the CS meets the NICE reference case requirements for economic evaluations is summarised in Table 21.

Table 21 NICE reference case requirements

NICE reference case requirements:	Included in submission	ERG comments
Decision problem as per NICE scope	Yes	Population and subgroups reflect scope (CS B.3.2.1). Fixed dose cemiplimab used for costing (CS B.3.2.3), but outcomes relate to weight-based dosing (integrated analysis, CS B.3.3). See section 4.3.2.2.
Comparator as listed in the NICE scope	Yes	Chemotherapy and BSC included, but with proxy data for BSC: chemotherapy in base case and EGFR inhibitor[9-12] scenarios (CS B.3.2.3). See section 4.3.2.2.
NHS and PSS perspective on costs	Yes	CS specifies NHS England perspective (CS B.3.2), but end of life care costs include social care costs (CS B.3.5.5). See section 4.3.8.2 below.
Costs should relate to NHS and PSS resources and be valued using the prices relevant to the NHS and PSS	Yes	Resource use based on expert judgement with unit costs from NHS reference costs 2016/17,[40] PSSRU 2017[41] and other sources[42] (CS B.3.5). Resource use appears high for routine NHS practice. Unit costs not up to date and include some errors: see section 4.3.8 below.
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	CS only gives pairwise ICERs (CS B.3.7.1). We also present fully incremental results but note that chemotherapy and BSC may not be considered as clinical options for all patients (section 4.3.10.1).
Synthesis of evidence on outcomes based on systematic review	Yes	
Time horizon long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	30 years, which is similar to full lifetime for cohort (CS Table 17).
Measuring and valuing health effects: expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life.	Yes	For base case, EORTC QLQ C30 data were mapped to EQ-5D-3L values (CS B.3.4). See section 4.3.6 below for discussion.
Source of data for measurement of health-related quality of life: Reported directly by patients and/or carers.	Yes	EORTC data collected from patients in cemiplimab phase II study.
Source of preference data: Representative sample of the UK population	Yes	Mapped to EQ-5D-3L UK tariff using Longworth et al. algorithm.[43]
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	

NICE reference case requirements:	Included in submission	ERG comments
Discount rate: 3.5% per year for costs and health effects	Yes	

4.3.2 Modelled decision problem

4.3.2.1 Population

The company's economic model is designed to evaluate outcomes for people with metastatic or locally advanced CSCC who are not candidates for curative surgery or radiotherapy (CS section B.3.2.1). This matches the NICE scope for this appraisal and the proposed marketing authorisation.

Model parameters used to characterise the population in the company's base case are shown in Table 22 below (CS section B.3.3.1). The age and gender split are used in the model to adjust utility and mortality rates as the cohort ages. Distributions of body weight and body surface area (BSA) are used to estimate dose and wastage for drug cost calculations. Values for these parameters were taken from the integrated analysis of the phase I and II cemiplimab studies (CS section B.3.3.1). The company argue that pooling phase I and II data is reasonable given the immaturity of the phase II data and similarities in the patients recruited to the two studies (CS Table 5). The CS does not include any sensitivity analyses to test the impact of uncertainty relating to population characteristics.

Table 22 Model parameters: patient characteristics at baseline

Input parameters		Base case Mean (sd)	DSA Range	PSA Distribution	Scenarios	Source
Age (years)		70.4	Not varied in sensitivity analyses			Pooled data from IPD phase I and phase II cemiplimab studies
Gender (% male)		85.0 [a]				
Weight (Kg)	Men	83.9 (15.3)				
	Women	62.1 (14.8)				
BSA (m^2)	Men	2.0 (0.2)				
	Women	1.6 (0.2)				

Source: adapted from CS Tables 18 and 41, BSA extracted from model by ERG.

BSA, body surface area; DSA deterministic sensitivity analysis range; IPD: individual patient data; PSA probabilistic sensitivity analysis distribution.

[a] This appears to be a miscalculation in the model (sheet 'Library PC'): with 92 men out of 108 in the integrated analysis set, the percentage should be 85.2%.

The statement in CS Table 18 and in the model ('Library PC' sheet) that these statistics are based on the safety analysis dataset (which includes 163 patients who received at least one

dose of cemiplimab) is inconsistent with the quoted sample size (n= 26+82=108). The ERG considers that baseline characteristic parameters should be based on all patients recruited to the cemiplimab studies, rather than a subset. The proportion of men in the safety analysis dataset (138/163, 84.7%) is similar to that in the integrated analysis dataset (92/108, 85.2%) (CS Table 5). Other baseline statistics in the model (mean age, gender, weight and BSA) are not reported for the safety analysis population. We note a small error in the model calculation of the proportion of men used in the base case (85.0%), compared with the numbers reported in the model (92/108, 85.2%). This does not have any impact on the model results.

Clinical experts advising the ERG suggested that the mean age and gender mix used in the company's base case are reasonably reflective of patients seen in routine practice with advanced CSCC not suitable for curative surgery or radiotherapy. However, our advisors noted considerable variation in the age of patients who they see, as shown by the wide range in the cemiplimab studies (38 to 96 years). Our advisors also suggest that the mean body weights from the cemiplimab studies may be higher than would be expected in clinical practice.

The company's base case uses pooled clinical data for people with locally advanced and metastatic disease, which the ERG's clinical advisors considered reasonable. The CS also presents cost-effectiveness results for separate subgroups with locally advanced and metastatic disease (CS Table 49; CS section B.3.8.3), as specified in the NICE scope. These scenarios use subgroup-specific PFS and OS survival curves but assume the same initial characteristics as for the whole population (Table 22 above). Baseline characteristics for patients with metastatic (n=75) and locally-advanced (n=33) disease in the cemiplimab integrated analysis are summarised in CS Appendix Table 44. It is difficult to draw clear conclusions about differences between the subgroups, as the numbers are small.

> **ERG conclusion**: Clinical opinion suggests that the baseline patient characteristics from the clinical studies used in the company's base case are reasonably reflective of the relevant population seen in the NHS, although there is uncertainty due to wide variations between patients presenting and lack of a UK cohort or disease registry. We conducted simple deterministic sensitivity analysis to assess the impact of uncertainty over age, gender mix and weight/BSA on cost-effectiveness results (see section 4.4.3 below).

4.3.2.2 Intervention and comparators

4.3.2.2.1 Cemiplimab

The base case analysis includes costs for cemiplimab at a fixed 350 mg dose administered as an IV infusion every three weeks, which reflects the anticipated marketing authorisation. The model uses clinical effectiveness data from the phase I study and groups 1 and 2 of the phase II study, in which patients received a weight-based dose of 3 mg/kg every two weeks. The company argues that pharmacokinetic analyses have demonstrated that the fixed and weight-based regimens achieve similar exposure and between-patient variability (CS section B.2.3.12), although the ERG questions the validity of this conclusion (Appendix 1). The use of different regimens for costing and clinical effectiveness introduces uncertainty and could be a potential source of bias. The model includes cost calculations for weight-based cemiplimab dosing, including wastage (most efficient use of vials but no sharing), which results in higher costs than the fixed dose, but the CS does not include this in scenario analyses.

ERG conclusion: The company use a fixed dose regimen to cost cemiplimab in their economic analysis. This is consistent with the proposed marketing indication but not with the clinical effectiveness data used in the model, which relates to a weight-based regimen. We conduct scenario analysis with costs as well as outcomes for weight-based cemiplimab dosing (section 4.4.3 below).

4.3.2.2.2 Comparators

The model includes two comparators, as specified in the scope:

- Chemotherapy: Costs and clinical outcomes from Jarkowski et al.[8] with cisplatin 100 mg/m^2 administered as an IV infusion once every three weeks with 5-fluorouracil 1,000 mg/m^2 administered on days 1-4 of the 3-week cycle (CS Table 32).
- BSC**:** Clinical outcomes using data for chemotherapy or EGFR inhibitors as a proxy for BSC and costs for packages of routine care and palliative surgery and radiotherapy in the pre- and post-progression health states (summarised in CS Tables 35 and 37). The same packages of services are assumed for patients in the cemiplimab and chemotherapy arms, except with a higher proportion of patients having post-progression palliative surgery after cemiplimab.

The company estimates that about 25% of patients with advanced CSCC unsuitable for curative treatment may be fit enough to have chemotherapy and that the remaining 75% of patients will receive BSC alone (CS section B.3.2.3).

The model is designed for pairwise comparisons of cemiplimab against each comparator, and full incremental results are not presented in the CS. This is appropriate if chemotherapy and BSC are not considered as treatment options for the same group of patients, but for completeness we also show full incremental results for the company's base case (section 4.3.10.1 below) and ERG corrections and additional analysis (sections 4.4.2 and 4.4.3).

ERG conclusion: The comparators in the company's model reflect the NICE scope: chemotherapy (cisplatin in combination with 5-fluorouracil) and BSC, although the same clinical effectiveness data, Jarkowski et al.,[8] are used for both comparators in the base case. The CS also presents a scenario with proxy data for BSC from pooled EGFR inhibitor studies. It is reasonable to assume that chemotherapy and BSC would not be considered as options for the same patients, so pairwise cost-effectiveness analysis is appropriate.

4.3.3 Model structure and assumptions

4.3.3.1 Overview of model structure

The company describes the model structure alongside the key model features in CS section B.3.2.2. They follow a conventional model design for cancer appraisals by developing a partitioned survival model in Microsoft Excel ®, consisting of three health states: pre-progression (PFS), post-progression and death. The model uses a one-month cycle and 30-year time horizon.

The company's illustration of the model is shown in Figure 1 (reproduced from CS Figure 22). Patients enter the model in the pre-progression health state. There they receive either cemiplimab or a comparator treatment (chemotherapy or BSC alone). From pre-progression, patients can transition to the post-progression health state or die. In the post-progression state, they receive only supportive care until death.

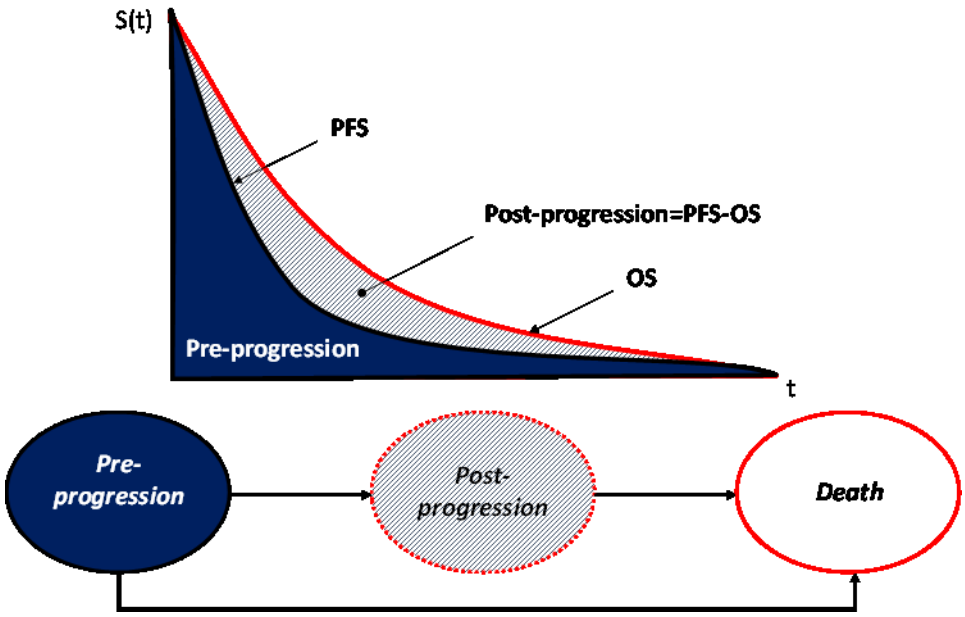

Figure 1 A schematic of the cost-effectiveness model
Source: reproduced from CS Figure 22

Movement of patients between the health states is governed by a set of PFS and OS curves for each intervention:

- The proportion of the cohort in the death state increases over time according to time-varying treatment-specific death rates defined by the OS curve or general population mortality (whichever is the higher).
- The proportion of the cohort in the pre-progression state decreases over time in line with the treatment-specific time-varying hazard rates, defined by the minimum of PFS and OS.
- The residual proportion of the cohort in the post-progression state is defined by the difference between the proportion of patients alive and the proportion of patients in the pre-progression state at each point in time.

The model estimates QALYs by multiplying utilities for the pre- and post-progression health states by the proportion of the cohort in those states and adding these over time. For the cemiplimab and chemotherapy arms, a one-off QALY loss is subtracted to reflect the impact of treatment-related adverse events at the start of treatment. Similarly, costs are estimated by applying one-off and monthly costs in accordance with the proportion of patients in the pre- and post-progression states. The model includes costs for: drug acquisition and administration for the duration of the cemiplimab and chemotherapy treatment; monitoring, supportive and

palliative care in the pre- and post-progression health states; and one-off costs for treatment of adverse events associated with cemiplimab or chemotherapy.

The company summarises how they have applied recommendations for partitioned-survival models in CS Table 16. They justify their rationale for use of this approach, arguing that it reflects the natural history of the disease, and provides structural flexibility and a good fit to the observed Kaplan-Meier data for PFS and OS. The company also considered alternative model structures:

- *Responder/ non-responder model*: The company states that they dismissed this idea because of the lack of evidence for survival rates by response status for the comparators and also the lack of evidence for utilities and costs for responders compared with non-responders (CS section B.3.2.2). We also note that this approach is likely to have increased rather than decreased uncertainty due to the wide credible interval around the odds ratios for response from the indirect comparison and the difference in estimates from the unadjusted (naïve) and MAIC population-adjusted analyses (which favoured cemiplimab) and the STC population-adjusted analysis (which favoured chemotherapy) (CS section B.2.9.3.3). Controversy around the validity of response measurement for PD-1 inhibitors may also add to this uncertainty.[44]

- *Mixture/ cure model*: This approach can provide a means to extrapolate long-term survival for interventions that induce a deep and lasting response ('cure') for a proportion of patients.[45] However, the company has rejected this approach due to the immaturity of data for cemiplimab. They note advice from UK experts (3 clinical oncologists and 2 health economists) that complex modelling approaches would not provide further clarity and would risk 'overfitting' the available data. We agree that in the absence of evidence to define and measure the proportion of patients with a distinctly better and lasting survival a mixture model would not help.

  ERG conclusion: We agree with the company's use of a simple, three-state partitioned-survival model structure. There is insufficient evidence to support a more complex response-based or mixture model, given the short follow-up for cemiplimab and sparsity of data for outcomes under current treatment options.

4.3.3.2 Summary of model assumptions

The company summarises and justifies key model features in CS Table 17. We comment on these and other important assumptions in Table 23 below.

Table 23 Model features

Factor	Company base case	Company's justification	ERG comments
Time horizon	30 years	Long enough to capture the lifetime of patients with advanced CSCC. (CS Table 17)	Agree
Model cycle length	Monthly model cycle (30.4 days), with half cycle correction	KM curves divided into monthly cycles to generate the discrete hazards for PFS and OS. (CS Table 17)	Agree
PFS and OS extrapolations	Independent survival curves fitted to cemiplimab and chemotherapy (Jarkowski[8]) data. Naïve comparison without adjustment for population.	To provide a closer fit to the actual PFS and OS data as observed in the clinical study. Estimates were also formally elicited from experts for validation, used in scenario analysis. (CS section B.3.3.2.1)	We consider the company's base case to be reasonable but explore a wider range of distributions in ERG analysis. See section 4.3.4 below for discussion.
Treatment duration	PFS for cemiplimab; 6 three-week treatment cycles for chemotherapy	Treatment duration was similar to PFS in phase II cemiplimab study. Expert opinion on chemotherapy. (CS section B.3.3.3.1)	Agree with treatment to progression for cemiplimab. Assumption that all patients complete 6 cycles of chemotherapy is unrealistic: a mean of 3 cycles is more realistic. See section 4.3.5.
Treatment stopping rule	Maximum of 22 months treatment with cemiplimab	As applied in phase II cemiplimab study (CS section B.3.3.3.1)	22 months reflects limit for groups 1 and 2 in Phase II protocol, but 24 months is more usual (e.g. NICE TA490[38]). We also consider scenarios with a 12-month limit and no stopping rule. Section 4.3.5.
Persistence of treatment effects	Cemiplimab PFS and OS hazards set equal to chemotherapy hazards 3 years from baseline	Evidence for continued effect of PD-1 inhibitors. 3 years gives conservative and clinically plausible long-term survival estimates. Alternative assumptions tested in scenario analysis. (CS section B.3.3.3.2).	Agree with 3-year base case, which is conservative relative to assumptions in other appraisals (e.g. NICE TA490 [38]). Uncertainty due to lack of evidence of long-term effect is reflected in a good range of company scenarios

Factor	Company base case	Company's justification	ERG comments
Source of utilities	EORTC-QLQ C30 values from phase II cemiplimab study mapped to EQ-5D-3L using Longworth algorithm[43]	As per NICE reference case. Data derived directly from patients in the largest advanced CSCC cohort study to date. Use of same utilities for cemiplimab and chemotherapy is conservative. Mapping algorithm has been validated (CS section B.3.4.5 and Appendix N)	We agree with the mapping approach but note that the results lack face validity: pre-progression utility is higher than for the general population and not adjusted for age. Uncertainty over the data and mapping is not accurately reflected. See section 4.3.6 for discussion and section 4.4.2 for ERG corrections.
Adverse events	One-off utility decrements and costs for grade 3 and 4 AEs with >=5% incidence for any study	AE rates for cemiplimab from pooled phase I and II studies excluding fixed dose (n=140) and from chemotherapy controls (n=325) with advanced HNSCC (Vermorken et al. 2013).[46] (CS section B.3.3.4) AE disutilities and costs identified from targeted review (CS sections B.3.4.4 & B.3.5.4)	The assumption of one-off costs and utility loss regardless of treatment duration is likely to favour cemiplimab. There is high uncertainty over AE rates. Some estimates (skin toxicity and immune reactions) are lower than expected for a PD-1 inhibitor. See section 4.3.6.
Perspective for costing	NHS England perspective	As per NICE reference case	Similar to NHS and PSS as social care costs are included for end of life care and other social services will be limited for this population.
Source of costs	Resource use assumptions from clinical advisory group. Unit costs from published sources at 2016/17 prices.[40-42]	As per NICE reference case. Clinical experts with experience of treating advanced CSCC in the NHS provided estimates of resource use (CS section B.3.5)	Resource use appears high for routine NHS practice. Unit costs are from appropriate sources but contain some errors and are not up to date. See 4.3.8. We applied 2018 unit costs (section 4.4.2) and ran a scenario analysis to reflect clinical advice on resource use (section 4.4.3).
Discounting	3.5% for costs and effects (QALYs)	As per NICE reference case	Agree

Source: Adapted from CS Table 17
AE: adverse event(s); HNSCC: head and neck squamous cell carcinoma; KM: Kaplan-Meier; PSS: Personal Social Services

ERG conclusions: Overall, the company's modelling approach and base case assumptions are reasonable and transparent. The CS gives a realistic view of the limitations of the evidence base and a fair discussion of the uncertainties. The base case uses relatively conservative assumptions and decisions are based on precedent where available. However, there are some exceptions that we discuss in the following sections.

4.3.3.3 Summary of input parameters

A summary of model input parameters is provided in CS Table 41, including:

- Baseline characteristics for the modelled cohort (CS section B.3.3.1)
- PFS and OS curves for cemiplimab, chemotherapy and BSC (CS section B.3.3.2)
- Treatment duration for cemiplimab and chemotherapy (CS section B.3.3.3)
- Incidence of adverse events (CS section B.3.3.4)
- Utilities for pre- and post-progression health states and disutilities for adverse events (CS section B.3.4)
- Resource use and costs for: drug acquisition and administration; monitoring, support and palliative care and treatment by health state; costs of treating adverse events (CS section B.3.5)

4.3.4 PFS and OS extrapolations

4.3.4.1 Data sources

The sources of data used to fit PFS and OS curves are:

- Cemiplimab: Integrated analysis of the phase I and phase II studies (n=108). This excludes those patients in the phase II study allocated to a fixed dose and those with follow-up less than 9 months from baseline. October 2017 data cut (median follow up 8.92 months (clarification question response A4). See section 3.1.3 above.
- Chemotherapy: Patients treated with cisplatin plus 5-fluorouracil in the Jarkowski study[8] (n=18).
- BSC: The base case employed a chemotherapy proxy from Jarkowski et al.,[8] which the company argues is conservative. The company also ran two scenario analyses with an alternative proxy data for BSC: i) estimates from four pooled EGFR inhibitor studies[9-12] (n=146); and ii) estimates from the pooled chemotherapy (Jarkowski[8]) and EGFR studies (n=164). These analyses are discussed in more detail in section 4.3.4.4 below.

This evidence consists of single-arm studies with no reliable adjustment for differences in populations and a very small retrospective chart review comprising the only evidence for chemotherapy and no direct evidence for BSC. Comparisons of treatment effectiveness from single arm studies are prone to bias due to differences in the study populations and context. The company discusses the limitations of the evidence base and of their attempts to adjust for population differences (CS section B.2.9.4). They report that they are conducting a retrospective chart review to collect data on current outcomes for the population, expected to report during 2019 (clarification question response A11).

> **ERG conclusion**: The ERG considers that the current evidence base is too weak to draw reliable conclusions about comparative effectiveness, and hence cost-effectiveness. The reliance on single-arm studies, problems with the MAIC and STC population adjustments and paucity of evidence for comparators means that the results are very uncertain and at high risk of bias. We do not believe that this uncertainty is fully reflected in the company's sensitivity and scenario analyses. For the future, the company's retrospective chart review might provide better evidence on real-life clinical outcomes. But in the absence of a randomised trial, assessment of comparative effectiveness requires collection and adjustment for all important prognostic factors.

4.3.4.2 Expert elicitation exercise

The company sought to supplement the sparse evidence with clinical opinion, elicited through the SHeffield ELicitation Framework (SHELF) approach (see CS Appendix M for a detailed description). The expert sample comprised oncologists and dermatologists with at least five years of experience, including treatment of skin cancer. For the elicitation on cemiplimab, experts needed to have experience treating members of the target population with cemiplimab. Participants were sent an evidence dossier in advance and interviewed using a web-based application. They were asked to estimate most likely values, and upper and lower plausible limits, for PFS and OS after 6, 7, 8, 9 and 10 years for chemotherapy and after 2, 3, 4, 5 and 10 years for cemiplimab. An anonymous online consensus meeting was held to discuss the results and the experts had the opportunity to revise their estimates. Six experts completed the elicitation for chemotherapy and nine for cemiplimab.

For the base case, the company only used the expert elicitation results 'visually and indirectly' to inform the choice of survival functions for PFS and OS. But they present a scenario with PFS and OS curves informed by expert expectations in a Bayesian model. This entailed fitting a normal distribution to the elicited survival proportions to create an artificial data set, which was pooled with observed Kaplan-Meier data. Parametric and fractional polynomial survival distributions were then fitted to this pooled dataset. The resulting scenario was considerably more favourable to cemiplimab than the base case analysis.

> **ERG conclusion**: The expert elicitation was clearly reported and appears to have been well-conducted. The exercise was double-blinded, but there is still potential for bias through the expert identification process, which included cemiplimab study investigators and their contacts. We therefore agree with the company's decision to use PFS and OS distributions fitted to empirical data alone for their base case analysis and we focus on these results in this report.

4.3.4.3 Naïve versus population-adjusted comparisons

The company note that the STC and MAIC results are susceptible to bias due to non-reporting of important prognostic variables for included studies (company clarification response A14). As always with single arm studies, there is also a risk that unknown or unmeasured prognostic factors cannot be accounted for. The company highlight particular problems with the MAIC: the reduced effective sample size for the cemiplimab studies (n=37), over reliance on data from a small number of individuals, and the limited face validity of the results (CS section B.2.9.4), as discussed in section 3.1.7 above.

Given the profound implications of extrapolating the uncertain population-adjusted survival estimates over 30 years, the company used the more conservative naïve comparison in their base case economic analysis. They also report an STC scenario analysis with adjustment for the two prognostic factors reported in the Jarkowski [8] study. This scenario results in more favourable cost-effectiveness results for cemiplimab than the base case analysis (CS Table 49).

> **ERG conclusion**: We agree with the company's reservations about the validity of the MAIC population adjustment. The limited availability of prognostic information from the Jarkowski[8] chemotherapy study also compromises the STC results. The ERG view is

therefore that the MAIC and STC do not offer any advantages over the naïve (unadjusted) comparison. Given that the naïve comparison was conservative in the company's base case, we believe the naïve PFS and OS estimates are more appropriate to inform the economic model. However, we stress that the naïve comparison results are susceptible to bias due to unknown differences in the study populations and are not conclusive.

4.3.4.4 Choice of proxy data for best supportive care

The CS systematic review did not identify any direct evidence for PFS or OS under BSC (see section 3.1.7.1 above). The company therefore used proxy data in their cost-effectiveness model: the Jarkowski[8] chemotherapy cohort in the base case; and pooled results from four EGFR inhibitor studies[9-12] (see Appendix 3), with and without the Jarkowski data, as scenarios. The chemotherapy base case is more conservative than the EGFR inhibitor proxy scenarios, yielding a higher incremental cost effectiveness ratio (ICER) for cemiplimab compared with BSC (CS Table 49). The company state that the EGFR inhibitor scenarios are also likely to be conservative, although they cite clinical advice that EGFR inhibitors are not considered to be effective (CS section B.3.2.3). Clinicians consulted by the ERG concurred with this view.

ERG conclusions: BSC is the only treatment option for patients who cannot tolerate chemotherapy. It is not possible to draw meaningful conclusions about the cost-effectiveness of cemiplimab for these patients in the absence of information about their current rates of progression and survival. We acknowledge the company's attempts to find alternative sources of information and agree that outcomes for chemotherapy and EGFR inhibitors are not likely to be worse than for BSC alone: so, these proxies should in theory provide conservative ICERs for cemiplimab. However, comparisons based on the available data sources are still highly uncertain, as they rely on small, uncontrolled samples.

4.3.4.5 Proportional hazards assumption

PFS and OS are modelled independently for each intervention (CS section B.3.3.2.1). Empirical evidence on whether the assumption of proportional hazards holds for OS or PFS is lacking (clarification question response A17). However, the company argues on theoretical grounds that proportional hazards are unlikely because of the different mechanisms of action of

cemiplimab and chemotherapy. They note that this point has been accepted in previous NICE appraisals for immunotherapies, including pembrolizumab and nivolumab for melanoma (TA366 and TA384) and atezolizumab for lung cancer (TA520).[37, 39, 47]

> **ERG conclusion**: We accept the company's argument that proportional hazards are not likely to apply for PFS or OS, due to the different mechanisms of action for PD-1 inhibitors and chemotherapy. It is therefore appropriate to fit independent PFS and OS curves to the single-arm study datasets.

4.3.4.6 Curve fitting process

PFS and OS distributions were fitted to digitised Kaplan-Meier data from the integrated phase I and phase II cemiplimab studies (naive and STC-adjusted comparisons), the Jarkowski chemotherapy study [8] and the EGFR inhibitor BSC-proxy studies.[9-12] The process of curve fitting is described in CS section B.3.3.2.2.

Fourteen parametric and fractional polynomial survival distributions were considered:[48-50]

- First order Weibull (p1=0) and Gompertz (p1=1);
- Second-order extensions of the Weibull and Gompertz with powers p2=-1, -0.5, 0, 0.5, or 1; and
- Log-normal and log-logistic parametric distributions.

These distributions allow for a variety of trends in hazard rates over time, including monotonic increases or decreases and U-shaped curves ('bath-tub' and 'rainbow'). Although the company did not explicitly include an exponential distribution, this is a form of Weibull distribution (with time coefficient equal to zero), which was included.[48]

The company selected curves for their base case and scenario analyses based on the following criteria:

- Development of hazards over time based on visual inspection and log-log cumulative hazard plots of study data (CS Figure 23).
- Goodness of fit measured by Deviance Information Criterion (DIC) statistics, a lower DIC indicating a better fit of the model to the observed data.

- External estimates of the plausibility of extrapolations beyond the study follow-up, based on the formal expert elicitation process (see section 4.3.4.2 above).

In practice, it is difficult to assess goodness-of-fit for the PFS and OS curves based on visual inspection or DIC statistics: the DIC values are similar across all of the fitted curves, with differences being too small to make meaningful distinctions (CS Tables 19, 20, 23 and 24). The clinical plausibility of extrapolations is also difficult to assess because of the lack of evidence. The company rule out some of the fitted distributions on the basis of trends over time, favouring distributions for cemiplimab with diminishing hazards (as has been shown for other PD-1 inhibitors), but disregarding extrapolations that plateau (as current data are insufficient to support a conclusion that rates fall to zero for a proportion of the cohort).

ERG conclusions: The company reports a well-structured process to fit and select PFS and OS survival curves for the economic model.[51] Nevertheless, it is difficult to draw conclusions about goodness-of-fit or plausibility of the extrapolations. We agree with the restriction to PFS and OS distributions with diminishing hazards, but which continue to decline over time. Beyond that, we suggest that a wide range of scenarios should be considered to reflect the high uncertainty over current outcomes and comparative effectiveness of cemiplimab.

4.3.4.6.1 Progression free survival

For their base case, the company chose Weibull distributions for cemiplimab and comparators, with log-normal and log-logistic scenarios. See CS Figures 24 and 29 (reproduced in Figure 7 and Figure 9 in Appendix 4 below) and CS Tables 19 and 23.

Table 24 below shows summary statistics for selected PFS distributions. For cemiplimab, we have omitted distributions that plateau (as these are overly optimistic given available data) and those that decline to zero after 2-3 years (which appear unrealistically pessimistic). This leaves 6 distributions, with 5-year PFS estimates between [redacted]. We ran additional ERG analyses for these more extreme scenarios (section 4.4.3).

Similarly, for chemotherapy, we have omitted distributions that plateau, leaving 8 distributions with 5-year PFS between 1% (Weibull) and 6% (log-logistic) – already included in the company's scenario analyses.

Table 24 PFS, selected distributions with decreasing but non-zero hazards

Distribution	Company analysis	ERG extra scenarios	DIC	Not capped by assumed duration of treatment effect or survival estimates			
				3 year	5 year	10 year	20 year
Cemiplimab (naive integrated analysis of Phase I and II studies)							
P1=0, P2=1		Scenario	57.03	[redacted]	[redacted]	[redacted]	[redacted]
P1=1, P2=0			56.82	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Base case		54.85	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Scenario		55.38	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Scenario		53.70	[redacted]	[redacted]	[redacted]	[redacted]
P1=0, P2=-1		Scenario	55.23	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy and BSC (Jarkowski cisplatin + 5-fluorouracil cohort)							
Weibull	Base case		33.60	8%	1%	0%	0%
Gompertz			33.65	8%	1%	0%	0%
P1=0, P2=-1			35.52	10%	3%	0%	0%
P1=0, P2=-0.5			35.39	10%	3%	0%	0%
P1=0, P2=0			35.73	11%	4%	1%	0%
P1=0, P2=0.5			35.52	12%	5%	1%	1%
Log-normal	Scenario		34.36	12%	5%	1%	0%
Log-logistic	Scenario		34.18	12%	6%	2%	1%
Source: Adapted by ERG from CS Tables 19 and 23 and the model							

4.3.4.6.2 Overall survival

The CS includes cost-effectiveness analysis for the following OS distributions: log-normal for cemiplimab (Weibull and Gompertz scenarios) and Gompertz for the comparators (P1=1, P2=0 and Log-normal scenarios). See CS Figures 25 and 30 (reproduced in Figure 8 and Figure 10 in 0) and CS Tables 20 and 24.

We consider some additional scenarios that reflect a wider range of extrapolations (Table 25). For cemiplimab, we report four distributions, with 5-year survival ranging from [redacted]. For chemotherapy we report 8 distributions, with 5-year OS from 16% (log-logistic) to 19% (p1=0, p2=0).

Table 25 OS, selected distributions with decreasing but non-zero hazards

Distribution	Company analysis	ERG extra scenarios	DIC	Not capped by assumed duration of treatment effect			
				3 year	5 year	10 year	20 year
Cemiplimab (naive integrated analysis of phase I and II studies)							
Log-logistic		Scenario	32.75	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Scenario		32.66	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Base case		31.51	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Scenario		31.76	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Company analysis	ERG extra scenarios	DIC	Not capped by assumed duration of treatment effect			
				3 year	5 year	10 year	20 year
Chemotherapy and BSC (Jarkowski cisplatin + 5-fluorouracil cohort)							
Log-logistic		Scenario	35.39	26%	16%	8%	3%
P1=1,P2=0	Scenario		35.22	23%	16%	13%	5%
Gompertz	Base case		34.01	26%	17%	12%	5%
P1=0, P2=-0.5			35.35	26%	19%	13%	5%
Weibull			35.90	30%	18%	7%	1%
Log-normal	Scenario		35.20	29%	18%	8%	2%
P1=0, P2=-1			35.46	26%	18%	12%	4%
P1=0, P2=0		Scenario	35.45	26%	19%	14%	5%
Source: Adapted by ERG from CS Tables 20 and 24 and the model							

4.3.4.7 Treatment effectiveness cap

Follow-up data for cemiplimab are currently limited (median 8.92 months, to a maximum of 28 months). The company cite evidence of continued response to PD-1 inhibitors after treatment discontinuation.[52, 53] They also note that NICE committees have accepted that this persistence of effects is clinically plausible given the mechanism of response, but have capped the assumed duration of relative benefit (e.g. 5 years for nivolumab in TA490).[38] In the base case analysis, the company set PFS and OS hazards equal to those for chemotherapy after 3 years, which they argue leads to conservative but clinically plausible long-term survival estimates. They also tested the impact of a good range of scenarios, from no further benefit after a maximum duration of treatment (22 months) to continued benefit throughout the 30-year time horizon. The model is sensitive to these changes (CS Table 49).

> **ERG conclusions**: The long-term effects of cemiplimab are currently unknown. The CS base case assumption that relative PFS and OS benefits (compared with chemotherapy) are maintained for 3 years is more conservative than assumptions in some other recent NICE appraisals for PD-1 inhibitors (e.g. 5 years for nivolumab in NICE TA490[38]). The company present a good range of scenarios: from no continued benefit after a maximum treatment duration of 22 months to continued benefits throughout the time horizon.

4.3.4.8 Summary of company PFS and OS extrapolations

We summarise the company's choice of PFS and OS distributions for the base case and scenario analysis in Table 26 below. The extrapolations used in the company's base case

analysis are shown in Figure 2 and Figure 3 below, including the 3-year cap on relative effects, which reduces the 5-year estimates for cemiplimab to [redacted].

ERG conclusions: The company's choices of PFS and OS distributions for their base case are reasonable. However, a number of other distributions have a very similar fit to the observed data, with equally plausible trends in hazards and long-term predictions of survival. We therefore extended the range of scenarios tested to illustrate the impact of a wide, but not implausible, range of extrapolations (see section 4.4.3 below).

Table 26 Company's choice of PFS and OS extrapolations

		PFS		OS	
Intervention	**Data source**	**Base case**	**Scenarios**	**Base case**	**Scenarios**
Cemiplimab	Phase I and II studies (naïve analysis)	Weibull	log-normal log-logistic	Log-normal	Weibull Gompertz
	Phase I and II studies (STC)		Weibull		Gompertz
	Phase II (naïve analysis)		Weibull		log-normal
	Phase II (naïve analysis) + expert opinion		P1=0, P2=-1		Gompertz
Chemotherapy	Jarkowski (CIS + 5-FU)	Weibull	log-normal log-logistic	Gompertz	log-normal P1=1, P2=0
	Jarkowski + expert opinion		Gompertz		log-normal
BSC	Chemo proxy (Jarkowski)	Weibull	log-normal log-logistic	Gompertz	log-normal P1=1, P2=0
	Pooled EGFR inhibitor proxy		Weibull		Gompertz
	EGFR inhibitor + Jarkowski		Weibull		Gompertz
	Jarkowski + expert opinion		Gompertz		log-normal
Source: ERG based on CS sections B.3.3.2.3 to B.3.3.2.6, Appendices M and P and model					

Figure 2 PFS extrapolations: company base case

Figure 3 OS extrapolations: company base case

4.3.5 Treatment duration

4.3.5.1 Cemiplimab

Protocols for the cemiplimab studies placed limits on the duration of treatment (CS Table 4):

- 22 months (96 weeks) for groups 1 and 2 in the phase II study (weight-based dosing);
- 12 months (52 weeks) for phase II study group 3 (fixed dose); and
- 11 months (48 weeks) in the phase I study.

The company explain their approach to modelling treatment duration in CS section B.3.3.3.2. CS Figure 33 shows Kaplan-Meier plots of time to treatment discontinuation (TTD) and PFS for the integrated cemiplimab analysis used in the model. The phase I study limit of 11 months treatment explains the fall in TTD at this time: restricting the plots to phase II study data shows a closer correspondence between TTD and PFS (CS Figure 34).

For their base case, the company assumes that cemiplimab treatment continues until progression (TTD=PFS), but with an upper limit of 22 months. They also present two scenarios:

- An adjustment for differences between TTD and PFS using a hazard ratio estimated from the phase II study data ([redacted]).
- A limit of 24 months, reflecting accepted stopping rules for immunotherapies in other recent NICE appraisals (e.g. TA520[47]).

The treatment stopping rule reduces the estimated cost of cemiplimab but not its effects, hence reducing ICERs. However, the limit on treatment effects (discussed in section 4.3.4.7 above) has the opposite effect. It is therefore important to consider the plausibility of the limits on treatment duration and effects together.

The ERG view is that the appropriateness and length of the stopping rule for cemiplimab is not clear-cut. The base case limit of 22 months is similar to the two year limit recommended in some NICE guidance for immunotherapies, founded on concerns about the safety of long-term treatment.[47] However, NICE Committees have expressed concerns about the lack of evidence for optimum treatment duration and difficulty in stopping treatment in practice when patients appear to be experiencing benefit.[37-39] For cemiplimab, although the 22-month stopping rule reflects the maximum treatment duration in the phase II study protocol, this limit has not yet

been reached, so does not inform the survival data currently used in the model, whereas these data have been influenced by the 12-month limit on treatment in the phase I study.

We therefore extended the range of assumptions about stopping rules and persistence of treatment benefits for cemiplimab in ERG scenario analyses, including;

- a 12-month stopping rule, with a 24-month limit on the duration relative treatment effects;
- no stopping rule, with a 36-month limit on duration of relative treatment effects; and
- no stopping rule, with no limit on the duration of relative treatment effects.

ERG conclusion: The company's base case assumptions on the duration of cemiplimab treatment are reasonable. The phase II study supports the assumption that TTD is similar to PFS; and the 22-month stopping rule reflects maximum treatment in the study protocol and is similar to precedent in other NICE guidance for PD-1 inhibitors (e.g. TA490[38]). However, the 22-month limit is not yet reflected in the integrated dataset used to estimate PFS and OS for the model, whereas the 11-month limit for the phase I study is. We therefore extend the range of stopping rules tested in ERG scenario analysis (see 4.4.3).

4.3.5.2 Chemotherapy

For chemotherapy, the company's base case assumes that all patients have 6 treatment cycles of 3 weeks (CS section B.3.3.3.3). In practice, not all patients complete all 6 cycles, so a scenario analysis assuming a mean of 3 treatment cycles is presented by the company. This reduces the estimated cost of chemotherapy, thus causing a modest increase in the ICER for cemiplimab compared with chemotherapy

ERG conclusion: The base case assumption that all patients complete the full 6 cycles of treatment is implausible. We consider that the scenario with a mean of 3 cycles of chemotherapy is more realistic

4.3.6 Adverse events

Modelled adverse event (AE) rates for cemiplimab and chemotherapy, and associated QALY loss and treatment costs are summarised in Table 27 below. No loss of QALYs or costs were assigned for adverse events under BSC.

Table 27: Adverse event rates, QALY loss and treatment costs used in model

Adverse event	AE rates (% of patients)		One off QALY loss [a]	One off cost (£)
	Cemiplimab	Chemotherapy		
Skin infection	1.1%	NR	0.010	£143.20
Hypercalcaemia	2.1%	NR	0.007	£1,139.92
Failure to thrive	7.7%	NR	0.006	£3,179.70
Fatigue	1.8%	NR	0.006	£3,179.70
Hypokalaemia	1.8%	7.1%	0.007	£1,139.92
Stomatitis or oral mucositis	NR	8.6%	0.013	£998.38
Neutropenia	NR	32.6%	0.007	£325.49
Anaemia	0.9%	14.5%	0.006	£1,273.72
Thrombocytopenia	NR	7.7%	0.009	£325.49
Febrile neutropenia	NR	5.2%	0.008	£2,688.94
Total QALY loss	[redacted]	[redacted]		
Total cost (£)	[redacted]	[redacted]		

Source: CS Tables 25, 26, 28 and 39, and Clarification Response Table 19 and 19
[a] Assumes one month for duration of all events. NR not reported

Grade 3 or 4 adverse event rates for cemiplimab were estimated from the integrated analysis excluding patients who received a fixed dose of cemiplimab (n=140). The company explain that this was intended to align the sources of data for treatment effects and adverse events. However, it means that adverse event rates in the model differ from those estimated from the full safety analysis set (n=163), as reported in CS Table 13 and in section 3.3.6 above. The ERG considers that the safety analysis set is a more appropriate source for estimating adverse event rates.

Jarkowski et al.[8] do not report adverse event rates. The company selected an alternative source based a 'targeted' literature review of studies for patients with advanced cancer treated with cisplatin and 5-fluorouracil (clarification question response B3) - no further details are given about the search. They selected the control arm (n=330) of the SPECTRUM trial reported by Vermorken et al. (2013),[46] based on expert advice that the population of advanced HNSCC would be the closest tumour type to borrow data from in the absence of data for people with advanced CSCC (clarification question response B3). The company state that the baseline

characteristics of patients in the cemiplimab studies and the Vermorken et al.[46] control arm are generally comparable, although the latter are younger (average age 59 years) with a worse performance status (69% with ECOG PS 1). We do not think that it is safe to conclude that the populations in the cemiplimab studies and Vermorken chemotherapy group are comparable.

The analysis only includes events with an incidence of Grade ≥3 of at least 5% in one of the studies (phase I or II cemiplimab, or Vermorken et al.). The way in which events were grouped means that no infections other than skin infection were included in the model, despite a collective incidence of Grade ≥3 infections of [redacted] from the safety analysis set (Table 17 above). This is similar to expected rates for immune checkpoint inhibitors already in use (pembrolizumab, nivolumab): a Consultee Submission for the current technology appraisal [Cemiplimab Professional Organisation Submission NCRI-ACP-RCP response] notes that potentially serious immunologically-based adverse effects would be expected in about 15% of patients, leading to drug withdrawal in about 7%. This view was supported by clinical advisors to the ERG.

Disutility values assigned to the adverse events were selected from previous NICE appraisals and QALY loss was calculated assuming a one-month duration of effects for all adverse events (CS Tables 27 and 28). Costs of treating adverse events were based on previous NICE appraisals, NHS Reference costs or PSSRU unit costs (CS Table 39). Adverse event costs and QALY loss were implemented as a one-off loss in the first model cycle. This omits the impact of lasting and late-onset adverse effects.

In addition to these problems, it is not clear whether the model is sensitive to assumptions about adverse event rates. The absolute cost and QALY loss associated with adverse events in the company's model are small. And based on a comparison with other PD-1 inhibitors in cancer, one would expect a higher incidence of adverse events with chemotherapy: The Xu et al.[34] network meta-analysis estimated odds ratios of 0.25 (95% CrI: 0.15 to 0.42) for grade 3/4 adverse events for nivolumab and 0.41 (0.21 to 0.79) for pembrolizumab, compared with conventional therapy. However, as noted above (section 3.3.6.4) the meta-analysis included heterogeneous studies and it is unclear how generalizable these results would be to patients with advanced CSCC.

ERG conclusion: There are limited data to support estimates of the incidence of adverse events for people with advanced CSCC treated with cemiplimab and chemotherapy. Problems with the company's approach mean that modelled adverse event-related costs and QALY loss are likely to be underestimated and may be biased in favour of cemiplimab (due to the omission of long-term and immune-related effects). We ran a conservative scenario analysis to illustrate model sensitivity to adverse events by applying related costs and QALY decrements at annual intervals in the cemiplimab arm.

4.3.7 Health related quality of life

Health state utility values for the base case were estimated by mapping EORTC QLQ-C30 scores collected from patients in the cemiplimab phase II study to estimate EQ-5D-3L (UK tariff) index scores (CS section B.3.4.3 and CS Appendix N).

The mapping algorithms used in the base case and scenario analysis (Longworth et al. 2014; and McKenzie and van der Pol 2009)[43, 54] were selected following a structured literature review described in CS Appendix N. Twelve mapping algorithms were identified for a range of cancers, of which five were capable of estimating EQ-5D-3L UK tariff scores (CS Appendix Table 50). Evidence for the validity of the algorithms was provided in two review articles (Doble and Lorgelly 2016 and Arnold et al. 2015).[55, 56] Both reviews identified the Longworth algorithm as performing well, and the McKenzie algorithm[54] was recommended by Arnold et al.[55]

In the phase II study, EORTC QLQ-C30 scores were collected from 65 participants at baseline and at least one follow-up visit, although baseline questionnaires had missing data for three cases. Of the remaining 62 patients, only eight experienced progression and 15 completed the questionnaire at the end of treatment. Thus, data are very sparse. The company applied a mixed effects model to the mapped phase II study data, with subject-level random intercepts and random slopes to adjust for baseline differences in utility (CS Appendix Tables 56 and 57). Predicted values for 'progressors' and 'non-progressors' provided the health state utility values for the base case and scenario (CS Tables 29 and 30).

We note an inconsistency in the reporting of standard errors for the mapped utilities in CS Tables 29 and 30, which were labelled as 'standard deviations' in CS Appendix Table 59. These values produce wide 95% limits used for sensitivity analysis in the model (from 0.47 to

0.98 for pre-progression utility) and it appears likely that these ranges reflect individual variation, This explains why the company identifies post-progression utility as the parameter associated with the greatest uncertainty for ICERs in one-way sensitivity analysis (CS Figures 43 to 46), which seems unlikely. We have adjusted the assumed standard errors for the health state utilities in ERG corrections (see section 4.3.10.2).

The company reports a systematic review to identify other sources of utility data for people with advanced CSCC (CS section B.3.4.1 and CS Appendix H). No relevant studies were identified, but the company based scenario analyses on values from NICE technology appraisals for other skin cancers (TA473[57] and TA489[36]) (see Table 28). Clinical experts advising the ERG suggested that basal cell carcinoma and Merkel cell carcinoma are the most comparable skin cancers to the target population. Data for the pre- and post-progression health states are not available from the appraisal of avelumab for Merkel cell carcinoma (TA517)[35], as these values were redacted in the committee papers.

Table 28: Utility estimates used in the company's model

Health state	Group	Mean	SE	Description	Source
Longworth et al. (2014)[43] algorithm					
Pre-progression	All	0.793	0.137 [a]	EORTC QLQ-C30 data mapped to EQ-5D	Cemiplimab phase II study
Post-progression	All	0.701	0.175 [a]		
Decrement	All	**0.092**			
McKenzie et al. (2009)[54] algorithm					
Pre-progression	All	0.815	0.158 [a]	EORTC QLQ-C30 data mapped to EQ-5D	Cemiplimab phase II study
Post-progression	All	0.719	0.203 [a]		
Decrement	All	**0.095**			
Alternative scenario from HNSCC submission (TA473[57])					
Pre-progression	Response/ stable	0.67	-	EXTREME trial[58] EORTC QLQ-C30 data mapped to EQ-5D	Hannouf *et al*.[59] NICE TA473[57]
Post-progression	All	0.52	-		
Decrement	All	**0.15**			
Alternative scenario from vismodegib submission for BCC (TA489[36])					
Pre-progression	laBCC	0.839	0.014	SF-36 data mapped to EQ-5D	ERIVANCE trial[60, 61]
	mBCC	0.819	0.017		
Post-progression	laBCC	0.757	0.037		
	mBCC	0.639	0.109		

Decrement	laBCC	**0.082**			
	mBCC	**0.180**			
Source: Adapted from CS Tables 29 and 30. laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma [a] Reported as standard deviation in CS Appendix Table 59,					

The model includes estimates of general population utilities for the gender mix and age of the cohort, based on a formula estimated from Health Survey for England data by Ara and Brazier (2011).[62] These are used to adjust post-progression utility as the cohort ages. However, the company notes that the resulting general population utility for the cohort (0.788) is less than the mapped estimate for the pre-progression state (0.793), and so they did not use the Ara and Brazier formula to adjust pre-progression utility (CS section B.3.4.5). We disagree with this approach, as the assumption that pre-progression utility does not decline with age lacks face validity and would bias the model in favour of cemiplimab (as the cohort spends longer in the pre-progression state). We applied an alternative approach in ERG corrections (section 4.4.2): setting the pre-progression utility equal to age-specific general population estimates and applying a utility decrement (0.793 – 0.701 = 0.092 in the base case) to estimate post-progression utility. We note that the pre/post progression decrements from the alternative sources used in company scenario analyses are reasonably consistent: from 0.092 in the base case to 0.180 for metastatic basal cell carcinoma in TA489.[36] We also present a scenario analysis using a multiplier to estimate post-progression utilities relative to pre-progression utilities (see section 4.4.3).

ERG conclusion: The company's method of estimating utilities from patient-reported EORTC QLQ-C30 data, mapped to EQ-5D-3L UK tariff values follows NICE recommendations and appears to have been well-conducted. However, the results are uncertain, because of the very small sample size, short follow-up and additional uncertainty around the mapping parameters. The results lack face validity, because the pre-progression utility is higher than estimates for the general population (adjusted for age and gender). However, the company's use of a fixed pre-progression utility in the model that does not decline with age is inappropriate, exaggerating the QALY gain from delayed progression attributed to cemiplimab. We corrected for this in ERG analyses. We also consider that, despite the uncertainties mentioned above, the company's sensitivity analysis around the utility parameters is likely to have over-estimated the importance of utility in driving cost-effectiveness results.

4.3.8 Resource use and costs

4.3.8.1 Drug acquisition costs

The monthly costs of drug acquisition are summarised in Table 29 (CS Tables 31 to 33). The company presents cemiplimab costs at list price and at the proposed Commercial Access Agreement (CAA) discount. Costs of chemotherapy and the weight-based cemiplimab regimen include wastage, calculated assuming most efficient use of vials but with no sharing of vials between patients. All drugs are costed at the specified dosage, assuming 100% intensity. This is unlikely to be realistic but should be conservative.

Table 29 Drug acquisition costs

Drug		Dose	£ per month	
			List price	Proposed CAA discount
Cemiplimab (fixed dose)		350 mg per 3 weeks	[redacted]	[redacted]
Cemiplimab (weight-based)		3 mg/kg per 2 weeks	[redacted]	[redacted]
Chemotherapy	Cisplatin	100 mg/m^2 per 3 weeks	£26	
	5-fluorouracil	1,000 mg/m^2 4 per 3 weeks	£15	
	Total		£41	
Source: CS section B.3.5.1.1 and CS Table 31				

4.3.8.2 Health care costs

The company conducted a systematic literature search to identify information about resource use and costs for adults with advanced CSCC (CS Appendix I), but this failed to identify any relevant information. Instead, they based estimates on opinions from clinical experts with experience of treating this patient group in the NHS. The resulting assumptions about resource use for the pre- and post-progression health states are summarised in CS Tables 35 and 37.

Clinical experts consulted by the ERG noted that in some respects the company estimates of resource use seemed unrealistic for routine NHS practice. They suggested that before progression, the following would be more usual:

- One consultation with an oncologist and blood tests very three weeks
- Wound management nurse and dressings 4 times per month, but 10 for patients with locally-advanced disease (33/108) and 2 for metastatic disease (75/108).

- Visits to both a tissue viability nurse and a clinical nurse every other month
- Fewer palliative radiotherapy treatments (50% once every 3 months)

Unit costs for the included resources were obtained from 2016/17 NHS Reference Costs and 2017 PSSRU estimates (CS Tables 36 and 38). We identified some errors and updated costs to 2017/18 prices.

Table 30 Unit costs in the company's model

Resource	Unit cost in model	ERG value 2017/18	Source
Health state resources			
Palliative surgery	£187	£195	NHS Reference cost 2017/18, JD07A-C
Oncologist visit	£173	£166	NHS Reference costs 2017/18, WF01A-370
GP visit	£38	£37	PSSRU 2018
Blood test	£1	£1	NHS Reference costs 2017/18 - DAPS04
Wound management nurse	£36	£59	PSSRU 2018, 1 hour band 5 community
Wound dressings	£10	£10	NICE TA489,[36] Vismodegib for BCC
Nurse tissue viability	£55	£61	NHS Reference costs 2017/18 - N25AF.
Clinical nurse specialist	£82	£89	NHS Reference costs 2017/18 - N10AF
Palliative RT	£107	£113	NHS Reference costs 2017/18, SC22Z OP
Complex palliative RT	£132	£141	NHS Reference costs 2017/18, SC23Z OP
District nurse	£37	£38	NHS Reference costs 2017/18 - N02AF
End of life care			
Hospital (health care)	£4,954	£4,422	Cost of health care, Round (2015). Inflated using new PSSRU HS index
Home (social care)	£2,190	£1,901	as above
Hospice (charity)	£492	£487	as above
IV chemotherapy administration			
Simple parenteral	£174	£229	NHS Reference costs 2017/18, SB12Z OP
Subsequent elements	£205	£289	NHS Reference costs 2017/18, SB15Z, OP
Adverse events			
Skin infection	£143	£145	Cost assumed to be the same as for cellulitis in NICE TA410,[63] inflated using new PSSRU HS index 2018
Hypercalcaemia	£1,140	£1,235	NHS reference costs 2017/18: KC05G,H,J,K,L,M,N
Failure to thrive	£3,180	£3,224	Assumed same as fatigue
Fatigue	£3,180	£3,224	NICE TA490,[38] inflated using new PSSRU HS index 2018
Infection	£261	£265	Assumed same as infection in NICE TA517,[35] inflated using new PSSRU HS index 2018
Infusion related reactions	£409	£423	NHS Reference cost 2017/18: WH05Z

Resource	Unit cost in model	ERG value 2017/18	Source
Rash, acne	£37	£37	Assumed same as rash, acne in NICE TA473[57] inflated using new PSSRU HS index 2018
Tumour bleeding	£65	£66	Assumed to be combined cost of Tissue Viability Nursing/Liaison and Cost of TNV (TA489[36]), inflated using new PSSRU HS index 2018
Hypokalaemia	£1,140	£1,235	NHS reference costs 2017/18: KC05G,H,J,K,L,M,N
Stomatitis or oral mucositis	£998	£1,012	Assumed same as nausea and vomiting in Brown 2013, two admissions each £443.54. Inflated using new PSSRU HS index 2018
Neutropenia	£325	£413	NHS reference costs 2017/18: WJ11Z
Anaemia	£1,274	£1,415	NHS reference costs 2017/18: SA01K, J,H,G
Thrombocytopenia	£325	£413	NHS reference costs 2017/18: WJ11Z,
Febrile neutropenia	£2,689	£2,727	NICE DSU 2007 (£2,286) inflated using new PSSRU HS index 2018
Source: CS Tables 36, 38, 41 and the economic model			

4.3.9 Model validation

The company describes their approach to model validation in CS section B.3.10. They state that they followed the recommendations by ISPOR and the Society for Medical Decision Making Joint Task Force for Modelling Good Research Practices to validate the cost-effectiveness model.[64] This guideline recommends four aspects of model validation: face validity, internal validity, cross validity and external validity.

For face validity, the company states that they discussed the proposed model structure along with parameters and assumptions in an advisory board meeting with UK key opinion leaders and validated inputs from UK and international experts. The CS also states that they verified the economic model in terms of calculations and programming; conducted a range of sensitivity analyses; and compared the model outputs with the source data, to ensure the model was technically valid. The latter comparisons showed that:

- In the **cemiplimab arm**, the PFS and OS survival estimates are comparable with the clinical data in the short-run i.e. up to 12 months but there remains significant uncertainty in the long-term estimates (i.e. 2 years and beyond). Further details are presented in CS Table 47.

- In the **chemotherapy arm**, the modelled survival estimates are comparable with those reported in the Jarkowski study[8] (details in CS Table 48), although there are intermittent over- and under-estimations. The company reports these differences to be not clinically significant.

The company stated that they had cross-validated the economic model by comparing the output with results of other models reported in the literature (CS B.3.10.1). The ERG agrees with the company's statement that it is not possible to compare the results of the model with previous economic evaluations in advanced CSCC. To overcome this shortcoming, the company compared the cost effectiveness results with the results in other types of tumour.

The CS states that an independent modelling team validated the economic model and compared it against the NICE reference case and previous NICE submissions in basal cell carcinoma and melanoma skin cancer. We assessed the current appraisal against the NICE reference case in section 4.3.1 above. Further, the company reports that a range of checks assessing credibility and face validity of the model were performed, although details are not provided.

> **ERG conclusion:** The company adhered to the ISPOR guidelines for validating economic evaluations. They reported details of techniques employed to evaluate the model predictions and outcomes. Whilst they suggest that the results of their validation checks indicated that the economic model outcomes are valid and credible, they do not explicitly report their findings.

4.3.10 Company's cost effectiveness results

4.3.10.1 Base case analysis

The company presents deterministic results for their base case analysis as pairwise ICERs for cemiplimab compared against chemotherapy and against BSC in CS Tables 43 to 46. We reproduce results with the proposed CAA price for cemiplimab in Table 31 below. Cemiplimab is estimated to cost an additional £43,740 per QALY gained compared with chemotherapy; and an additional £46,239 per QALY gained compared with BSC.

In a full incremental analysis, chemotherapy is dominated by BSC as it is more expensive with marginally lower QALYs (due to the use of the same effectiveness data as for chemotherapy from the Jarkowski study[8]). However, we note that the incremental analysis is not relevant if in practice the two comparators would not be considered as options for individual patients (e.g. depending on fitness for chemotherapy).

Table 31 Cost effectiveness: company's base case (proposed CAA price for Cemiplimab)

	Total costs (£)	Total QALYs	Pairwise ICERs (cemiplimab vs. comparator) (£ per QALY gained)	Incremental analysis (£ per QALY gained)
BSC	[redacted]	[redacted]	£46,239	-
Chemotherapy	[redacted]	[redacted]	£43,740	Dominated
Cemiplimab	[redacted]	[redacted]	-	£46,239
Source: CS Tables 44 and 46				

4.3.10.2 Probabilistic sensitivity analysis

The company assessed parameter uncertainty of their base case model by conducting probabilistic sensitivity analysis (PSA). Assumptions used to characterise uncertainty are described in CS Table 41 within CS section B.3.6. Shape and scale parameters for the PFS and OS survival distributions were randomly drawn from CODA samples based on 1,000 iterations from the Markov Chain Monte Carlo analysis. Adverse event incidence rates and utility values and decrements were drawn from beta distributions, and costs from gamma distributions. Standard errors for adverse event rates were estimated from reported values for the cemiplimab phase I and II studies (naïve pooling) and the Vermorken et al. study for chemotherapy.[46] However, standard errors for the adverse event disutilities and for all cost parameters are not empirically based but were just assumed to be 10% of the mean.

As noted in section 4.3.6 above, there appears to be an error in the characterisation of uncertainty around the health state utility values. The model uses values reported in the CS as standard deviations (CS Appendix Table 57) rather than standard errors to model uncertainty around the mean values. This means that the sampled values in the PSA would reflect individual variation, rather than population level uncertainty.

The company illustrates the PSA results as scatterplots and cost-effectiveness acceptability curves (CEACs) in CS Figures 35 to 42 (CS section B.3.8.1). The PSA results are comparable with the deterministic base case results (details in CS Appendix Q). With the proposed CAA price, the CS states that at a willingness to pay threshold of £50,000 per QALY, the probability of cemiplimab being cost-effective would be 55% when compared against chemotherapy and 50% when compared against BSC. The company acknowledges the high degree of uncertainty associated with the current evidence, suggesting that this would decline if further collection of data occurs on the Cancer Drugs Fund.

4.3.10.3 One-way sensitivity analyses

The company reports ranges used for parameters in their one-way sensitivity analyses in CS Table 41 (low and high values). These ranges are set at the 2.5th and 97.5th percentiles of the assigned probabilistic distributions for the included parameters. This results in reasonable ranges for most parameters, but the wide ranges used for the mean health state utilities do not appear plausible: 0.469 to 0.980 for pre-progression; and 0.312 to 0.963 for post-progression. It appears that these ranges reflect an error in using standard deviations rather than standard errors to characterise uncertainty around the estimated means.

The results of the one-way sensitivity analyses are illustrated in tornado plots in CS Figures 43 to 46. Disregarding the results for health state utility parameters, which we believe to be based on an unrealistically wide range of uncertainty around the mean, the tornado plots show that the economic model was most sensitive to the parameters defining OS curves for cemiplimab, chemotherapy and BSC. The very wide ranges for OS estimates indicate the significant impact of uncertainty around the prediction of OS for the treatment as well as the comparator arms. Parameters defining PFS and the monthly costs in the pre- and post-progression states also influence the base case ICERs, but to a lesser extent.

> **ERG conclusion**: The company's probabilistic and deterministic sensitivity analyses demonstrate a high level of uncertainty around their cost-effectiveness results. Taking account of the proposed CAA price, the estimated probability that cemiplimab is cost-effective is 55% in comparison with chemotherapy and 50% in comparison with BSC. Parameter uncertainty is driven primarily by uncertainty over rates of overall survival with cemiplimab and the comparators and how these are expected to change over time. We emphasise that these sensitivity analyses do not incorporate structural uncertainties over

modelling assumptions or the likelihood of confounding due to the nature of the evidence base.

4.3.10.4 Scenario analyses

The company conducted a range of scenario analyses to assess the impact of structural uncertainties over their base case assumptions. A summary of the company's scenarios is presented in CS Table 49 and below in Table 37.

The company concludes that most of the scenarios result in ICERs below £50,000 per QALY when the proposed CAA price is used. We note the following exceptions:

- No continued effectiveness advantage for cemiplimab beyond the maximum treatment duration of 22 months (PFS and OS hazards set equal to those for chemotherapy after this time). As might be expected, this reduces the estimated QALY gain compared with the base case which assumes that relative effects persist for a total of three years.
- Constant hazard after 22 months for cemiplimab. This is more conservative than the base case (Weibull for PFS and Log-normal for OS), which have decreasing hazards.
- Log-normal OS distribution for chemotherapy. This is a more optimistic extrapolation, yielding better long-term survival with chemotherapy than the base case Gompertz (5% vs. 1% at 5 years).
- Health state utilities from the EXTREME trial (platinum based chemotherapy plus cetuximab for head and neck cancer) [59], as used in TA473. These estimates are lower, with a larger difference between pre- and post-progression (0.67 and 0.52 respectively, decrement 0.15) than the estimates from the cemiplimab phase II study used in the company's base case (0.793 and 0.701, decrement 0.092).
- Shorter time horizons (10 and 5 years).
- Higher discount rates for costs and effects (6% per year).

ERG conclusion: The company's scenario analyses illustrate the sensitivity of results to: the use of data from the phase I cemiplimab study in addition to phase II data; the assumed persistence of effects for cemiplimab beyond the maximum treatment duration of 22 months; overall survival with chemotherapy; and the source of health state utility estimates. We consider that the company has been selective in the scenarios that they present, considering only a narrow range of survival functions. We explore some additional scenarios in section 4.4.3 below.

4.4 Additional work undertaken by the ERG

4.4.1 ERG model validation

4.4.1.1 Model verification procedures

The ERG conducted a range of manual checks to verify model inputs, calculations and outputs ('white box' tests), including:

- Cross-checking of parameter inputs against values in the CS and cited sources
- Tracing input parameters from the 'Library', 'Input' and 'PSA input' sheets, through to the model engines (Arm 1, Arm 2 and Arm 3) sheets
- Checking QALY and cost calculations in the model engine sheets
- Extreme value tests for costs and utilities
- Checking all model outputs against results cited in the CS, including the base case, PSA and DSA and we manually ran scenario analyses.

4.4.1.2 Comparison with long-term survival data

The company compared the extrapolated OS estimates with UK general population mortality. We confirm that the general population survival lies above the OS curves for the modelled population for all scenarios.

The company notes that there are no external data for comparison of long-term survival with cemiplimab for the population of interest under current treatment. They compared their modelled survival estimates with those for other immunotherapies[65, 66] (CS section B.3.7.1). However, these estimates relate to a different population: people with advanced melanoma.

Due to this sparsity of available data, we compare survival estimates for chemotherapy against survival for patients with metastatic Merkel cell carcinoma from NICE TA517[35] in Table 32 (based on our clinical experts' advice that Merkel cell carcinoma is a reasonable proxy for advanced CSCC). However, we emphasise that these comparisons should be treated with caution due to the different populations and chemotherapy. We also emphasise the TA517 NICE committee's conclusion was that the survival estimates were highly uncertain and therefore it was not possible to draw robust conclusions.

Table 32 Comparison of chemotherapy OS in the current appraisal with NICE TA517

	5 year	10 year
NICE TA517[a]	0%	0%
Current appraisal	16%	7.5%
[a] Data extracted from pooled EU and US OS data for patients in the treatment-experienced group (Figure 40 in ERG report of TA517). Long-term OS data were extrapolated using Gompertz distribution.		

To assess the above predictions, we present a comparison of the OS curves fitted to the chemotherapy arm in the Jarkowski study[8] against long-term survival data from an external source by Eigentler et al.[67] (see Figure 4). The external data source included 10 years of follow up from a German cohort that included 1,434 patients (with mean age of 78 years) who were diagnosed with invasive CSCC. The cohort in this study included curable as well as non-curable CSCC patients, unlike the population of interest in the current appraisal. Nonetheless, we view that this study provides a relevant reference for the expected upper limit of OS for the population in the current appraisal.

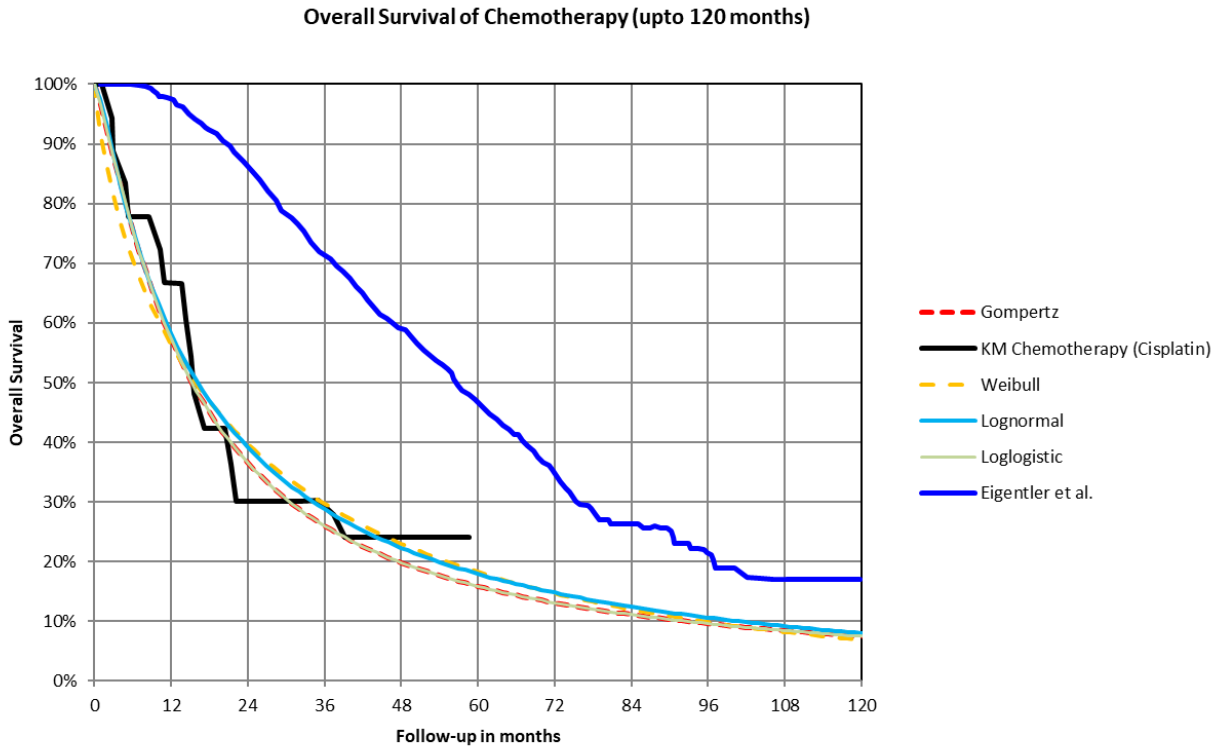

Figure 4 Comparison of OS with external source (Eigentler)
External source: Eigentler et al.[67]

Cancer Research UK indicates that the cure rates for patients with CSCC whose cancer has spread to the lymph nodes or to other parts of the body are high, but does not report statistics. Three clinical experts advising the ERG suggested 5-year survival rates in this patient population receiving chemotherapy are likely to range between 5% and 20%, depending on the cancer staging.

4.4.1.3 Comparison with other model outcomes

The company did not identify any other economic models relevant to the decision problem, except previous NICE Technology Appraisals for immunotherapies in other tumour types (section 4.2 above). Our clinical experts suggested that patients with advanced CSCC are expected to have a similar prognosis compared to those with advanced Merkel cell carcinoma. Due to lack of other relevant models, we compared the modelled outcomes in the current appraisal with those in treatment-experienced patients estimated in NICE TA 517.[35] We chose this sub-group for comparison as these patients are presumably more advanced, and hence more appropriate for the population not suitable for curative treatments. These provide sources for cross-validation of results from the company's base-case analysis. Modelled estimates of mean discounted overall life years and QALYs are summarised in Table 33.

Table 33 Comparison of modelled outcomes

Treatment	Outcome	Discounted mean (years)	
		TA517 (ERG assumptions for treatment-experienced)	**Submitted model** (base case)
Cemiplimab	Life years	--	[redacted]
	QALY	--	[redacted]
Chemotherapy	Life years	0.41	[redacted]
	QALY	0.30	[redacted]
BSC	Life years	0.41	[redacted]
	QALY	0.31	[redacted]
Source: Table 79 in ERG Report for NICE TA517[35]			

There are methodological differences between the models in the current appraisal and in NICE TA517,[35] alongside differences in the decision problem. TA517 relates to the sub-group of patients with Merkel cell carcinoma who have had one or more lines of treatment for metastatic disease. The results presented in the above table are for the treatment-experienced sub-group.

4.4.2 ERG corrections to company analyses

We identified and corrected some errors in the company's original model. Details are shown in Table 34.

Table 34 ERG corrections to the company's model

Aspect of model	Problem	ERG Correction
Utility calculations	Misleading method of adjusting health state utilities for age: pre-progression utility stays constant throughout the time horizon while post-progression utility is reduced as the cohort ages.	Pre-progression utility set equal to general population estimate (adjusted for age); decrement applied to estimate post-progression utility
	Use of standard deviations rather than standard errors to characterise uncertainty around the mapped utility estimates for pre-progression and post-progression health states. Exaggerates importance of uncertainty over health state utilities in deterministic and probabilistic sensitivity analyses.	Standard errors estimated from standard deviations, with assumed sample size of 62. This is conservative, as it does not take account of repeated observations.
Unit costs	Corrections of unit costs	See Table 30 above
Proportion of men in the population	Small error in calculation in model	The correction had no effect on the cost-effectiveness results.

4.4.2.1 Base case

Deterministic base case results with ERG corrections at the proposed CAA prices are shown in Table 35. The ICERs are higher than reported in CS Table 44 and 46 (Table 31 above):

- £49,155 compared with £43,740 for the comparison with chemotherapy;
- £52,539 compared with £46,239 for the comparison with BSC.

These increases are driven by both higher costs (due to uprating of unit costs to 2018 prices) and lower QALY gains (due to addition of age-adjustment for pre-progression utility). These changes are more pronounced for cemiplimab, because it is associated with longer predicted pre-progression and OS than the comparators.

Table 35: Cost effectiveness: ERG corrected company base case, deterministic (proposed CAA price for cemiplimab)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£52,539
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£49,155
Cemiplimab	[redacted]	[redacted]	-	-	

4.4.2.2 Probabilistic sensitivity analysis

Results from the probabilistic sensitivity analysis are similar to the deterministic results (Table 36). The estimated probability that the ICER for cemiplimab would be less than £50,000 per QALY gained is 43% compared with chemotherapy, and 34% compared with BSC.

Table 36: Cost effectiveness: ERG corrected company base case, probabilistic (proposed CAA price for cemiplimab)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£55,772
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£52,284
Cemiplimab	[redacted]	[redacted]	-	-	

4.4.2.3 One-way deterministic sensitivity analysis

The tornado diagrams in Figure 5 and Figure 6 illustrate the impact of varying input parameters on ICERs for chemotherapy and BSC. The parameters that define the OS extrapolations for cemiplimab and the comparators are the largest contributors to uncertainty over cost-effectiveness.

Our corrections to the standard errors for the utility parameters reduced the ranges tested in one-way sensitivity analysis. These were 0.758 to 0.826 for pre-progression survival and 0.656 to 0.744 for post-progression survival. This reduced their apparent impact on ICERs, which we consider to be more realistic.

Figure 5: Tornado plot for cemiplimab vs chemotherapy: ERG-corrected company base case (proposed CAA price for cemiplimab)

Figure 6: Tornado plot for cemiplimab vs BSC: ERG-corrected company base case (proposed CAA price for cemiplimab)

4.4.2.4 Scenario analyses

Our revisions to the company's scenario analyses are shown in Table 37. The direction and magnitude of the effects on estimated ICERs are similar to those presented by the company (CS Table 49). The key effects are summarised below:

- *Duration of treatment*: Cemiplimab appears less cost-effective with a shorter duration (and hence cost) of treatment, e.g. with a 24 rather than 22 month stopping rule or when time on treatment follows observations in the phase II study (TTD<PFS).

- *Persistence of benefits*: Results are also sensitive to assumptions about how long the benefits of cemiplimab last, with higher ICERs when effects are assumed to last for only 22 months, rather than 36 months; and lower ICERs for scenarios with a more durable effect (up to 5 years or continuing throughout the 30-year time horizon).
- *Survival extrapolations*: ICERs are sensitive to changes in overall survival curves, being lower with more optimistic predictions for cemiplimab (e.g. using the Gompertz distribution) or some less favourable predictions for chemotherapy (the fractional polynomial with P1=1 and P2=0). However, the effect of the OS curve for chemotherapy is not always obvious, because after 3 years, hazards for cemiplimab are set equal to those of chemotherapy.
- *Data sources and analysis*: Changes to the data sources for PFS and OS lead to some large changes in ICERs. Excluding the phase I cemiplimab study data increases ICERs above £60,000 per QALY. The STC data and elicited estimates from experts reduce the ICER estimates.

Table 37: Company scenario analyses: ERG-corrected (proposed CAA price for cemiplimab)

Base case input	Scenario	ICER versus chemotherapy	ICER versus BSC
Base case results		£49,155	£52,539
Comparative efficacy: Naïve	STC	£43,622	£45,949
22 month stopping rule	24 month stopping rule	£51,108	£54,498
Assumption regarding continued treatment benefit following the 22-month treatment cap: 3-year cap	Continued benefit	£41,821	£44,338
	22-month cap	£62,119	£67,062
	5-year cap	£43,124	£45,792
	Constant hazard after 22 months	£54,784	£58,876
	Waning effect between 22 months to 5 years	£46,376	£49,429
Integrated analysis of phase I and phase II trials	Phase II study	£63,058	£68,355
Alternative curve fits for cemiplimab: OS	Gompertz	£42,702	£45,328
	Weibull	£49,301	£52,703
Alternative curve fits for cemiplimab: PFS	Lognormal	£48,864	£52,245
	Log-logistic	£48,789	£52,176
Alternative curve fits for chemotherapy: OS	Lognormal	£61,875	£66,800
	Second-order fractional polynomial P1=1, P2=0	£46,524	£49,591
Alternative curve fits for chemotherapy: PFS	Lognormal	£48,751	£52,075
	Gompertz	£49,149	£52,497

Base case input	Scenario	ICER versus chemotherapy	ICER versus BSC
Cemiplimab time on treatment equal to PFS	Adjustment for time on treatment	£43,718	£47,086
Chemotherapy: 6 treatment cycles	3 treatment cycles	£50,498	£52,539
Utilities: EQ-5D mapped from Phase II EORTC-QLQ30, Longworth algorithm	McKenzie algorithm	£49,341	£52,739
	HNSCC (TA473[57])	£52,666	£56,304
	ERIVANCE trial[60, 61] laBCC	£48,587	£51,930
	ERIVANCE trial[60, 61] mBCC	£54,691	£58,476
Population: Pooled	Locally advanced	£48,446	£51,137
	Metastatic	£51,058	£55,091
Time Horizon: 30 years	20 years	£49,978	£53,484
	10 years	£58,972	£63,645
	5 years	£80,068	£87,462
Discount rate: 3.5% for costs + QALYs	0%	£43,474	£46,066
	6%	£53,299	£57,281
	1.5%	£45,879	£48,803
Efficacy of BSC: equal to chemotherapy	Pooled EGFR studies	N/A	£44,923
	All studies pooled	N/A	£46,022
Long term extrapolations of cemiplimab, chemotherapy and BSC: based on the integrated analysis of cemiplimab studies and Jarkowski[8] study	Based on the cemiplimab phase II study + experts' elicitation and Jarkowski[8] study + experts' elicitation	£36,028	£37,837
laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma			

4.4.3 ERG additional analyses

4.4.3.1 ERG scenario analyses

We present a summary of our additional scenario analyses in Table 38. A full summary of ERG observations on key aspects of the company's economic model is also provided in Appendix 5.

Table 38 ERG additional scenarios

Aspect of the model	Company's base case (scenarios)	Additional ERG scenarios	ERG comments
Population	Gender: 85% male	75% to 95% male	To explore uncertainty over patient characteristics in practice. Clinical opinion is that cemiplimab study population is reasonably representative, but that there is wide variation. No evidence from UK cohort or disease registry.
	Mean age: 70.44 years	60 to 80 years	
	Mean weight (SD): • Men: 83.9 (15.3) • Women: 62.1 (14.8)	+/- 10%	
	BSA, mean (SD): • Men 2.0 (0.2) m^2 • Women 1.6 (0.2) m^2	+/- 10%	
Intervention	Cemiplimab costs for fixed dose (350mg per 3 weeks). Effects for weight-based regimen (3mg/kg every 2 weeks), as in phase I study and groups 1 and 2 of the phase II study	Cemiplimab costs for weight-based regimen, assuming no vial sharing, and varying mean weight +/- 10%	Fixed dose costing reflects the anticipated marketing authorisation but is inconsistent with the weight-based regimen in clinical evidence. We also tested sensitivity of the weight-based cost scenario to mean weight for the population
PFS	Cemiplimab: Weibull (log-normal & log-logistic)	• p1=0; p2=1 • p1=0; p2=-1	Base case PFS and OS distributions are reasonable. However, a wide range of extrapolations have a similar fit to the data. We extended the range of distributions in scenario analyses to illustrate the impact on cost-effectiveness.
	Chemotherapy: Weibull (log-normal & log-logistic)	None	
OS	Cemiplimab: log-normal (Weibull & Gompertz)	• Log-logistic	
	Chemotherapy: Gompertz (P1=1/P2=0 & log-normal)	• Log-logistic • P1=0, P2=0	
Utilities	PFS 0.793 at all ages; Progressed 0.703 to 0.551 from age 70 to 100 years (McKenzie algorithm; EXTREME trial for metastatic head and neck SCC TA473; and locally	• Utility multiplier for progression: PFS (0.788 to 0.611); post-progression (0.697 to 0.540)	ERG corrections include: general population utility for PFS (0.788 to 0.611) with a fixed decrement of 0.092 on progression (0.696 to 0.519). The ERG additional scenario uses a utility multiplier (0.884) to estimate post-progression

Aspect of the model	Company's base case (scenarios)	Additional ERG scenarios	ERG comments
	advanced and metastatic BCC ERIVANCE study)		utilities relative to PFS values.
AE costs and effects	One-off QALY loss / cost for cemiplimab ([redacted]) & chemotherapy ([redacted])	• QALY loss & cost for cemiplimab ([redacted]) each year	Extreme scenario to test sensitivity of the model to changes in relative AE rates and ongoing AE impact with cemiplimab
Treatment stopping and persistence of effects	Cemiplimab stops at progression or maximum of 22 months. Relative effects for 3 years. (24-month cap on treatment. Persistence of effects from 22 months to time horizon)	• Treat for 1 year, effects for 2 • Treat for 2 years, effects for 3 • No stopping rule, 3-year effects • No stopping rule, no limit on effects	Base case is reasonable, as the phase II study protocol limits treatment to 22 months (group 1 and 2). However, this does not influence data in the model and phase I study had an 11-month limit on treatment.
	All patients complete 6 cycles of chemotherapy (mean 3 cycles)	None	The assumption that all patients complete the full 6 cycles of treatment is implausible: 3 cycles is more realistic
Resource use	Health state resource use for pre and post progression based on expert opinion	Fewer outpatient and nurse visits and palliative RT pre-progression	To be more reflective of clinical practice in the UK
AE: adverse events; BSA: body surface area			

Results of our scenario analyses are shown in Table 39.

ERG conclusion:

- There is a modest increase in ICERs when the costs of cemiplimab are estimated for the weight-based regimen on which the clinical effectiveness data were based. As might be expected, this finding is sensitive to the mean weight of the population.
- A more optimistic survival extrapolation for chemotherapy increases the ICER estimates. The impact of using other OS and PFS extrapolations is smaller than we had anticipated, due to the impact of the 3-year treatment effectiveness cap.
- The model is highly sensitive to the assumed duration of treatment and persistence of benefits, with ICERs below £50,000 per QALY when we assume only 1 year of treatment;

and persistence of effects for a further year, to over £80,000 per QALY if we do not limit the duration of treatment pre-progression or the assumed duration of effects.

- Reducing health state resource use, and hence costs, causes a small reduction in estimated ICERs.
- Assuming a constant proportional reduction in utility on disease progression, rather than a constant absolute decrement, gives a small increase in the estimated QALY gains from cemiplimab and hence a small reduction in ICERs.

Table 39 ERG scenarios: ERG-corrected company base case, deterministic (at CAA price for cemiplimab)

Scenario	Comparator	Total cost	Total QALYs	Pairwise ICERs (cemiplimab vs comparators)
Company base case (ERG corrected)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£49,155
	BSC	[redacted]	[redacted]	£52,539
Patient characteristics				
Gender: 75% male	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£49,315
	BSC	[redacted]	[redacted]	£52,707
Gender: 95% male	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£49,005
	BSC	[redacted]	[redacted]	£52,378
Mean age: 60 years	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£42,462
	BSC	[redacted]	[redacted]	£45,201
Mean age: 80 years	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£60,123
	BSC	[redacted]	[redacted]	£64,654
Weight-based cost for cemiplimab				
Costs for weight-based regimen	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£52,437
	BSC	[redacted]	[redacted]	£55,831
Costs for weight-based regimen with higher mean patient weight (+10%)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£85,090
	BSC	[redacted]	[redacted]	£88,583
PFS extrapolations				
Cemiplimab: p1=0; p2=1	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£49,381
	BSC	[redacted]	[redacted]	£52,766
Cemiplimab: p1=0; p2=-1	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£50,082
	BSC	[redacted]	[redacted]	£53,418

Scenario	Comparator	Total cost	Total QALYs	Pairwise ICERs (cemiplimab vs comparators)
OS extrapolations				
Cemiplimab: log-logistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£51,635
	BSC	[redacted]	[redacted]	£55,314
Chemotherapy: p1=0; p2=0	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£48,449
	BSC	[redacted]	[redacted]	£51,743
Chemotherapy: log-logistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£58,479
	BSC	[redacted]	[redacted]	£62,992
Treatment duration: cemiplimab				
Treatment cap at 1 year with effects for 2 years	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£43,600
	BSC	[redacted]	[redacted]	£48,121
No treatment cap with effects for 3 years	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£69,757
	BSC	[redacted]	[redacted]	£73,204
No treatment cap or limit on duration of effects	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£82,468
	BSC	[redacted]	[redacted]	£85,076
Health state utilities				
Multiplier for utility loss on progression	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£48,829
	BSC	[redacted]	[redacted]	£52,190
Adverse events for cemiplimab				
Annual recurrence of adverse event cost and QALY loss for duration of treatment effects (3 years)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£49,456
	BSC	[redacted]	[redacted]	£52,843
As above + equal adverse event QALY loss and costs for cemiplimab and chemotherapy	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£50,150
	BSC	[redacted]	[redacted]	£53,561
Resource use				
Reduced resource use before progression (ERG scenario based on clinical advice)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£47,038
	BSC	[redacted]	[redacted]	£50,415

4.4.3.2 ERG preferred assumptions

The ERG considers the current evidence base to be insufficient to draw reliable conclusions about comparative effectiveness, hence cost-effectiveness. We have conducted a range of scenario analyses to address some of the uncertainty; however we do not believe the degree of uncertainty is fully reflected through these analyses. Given the limited data, we chose not to

present a single ERG 'base case'. Instead, we outline below two scenarios reflecting sets of optimistic and pessimistic assumptions drawn from what we consider to be plausible options (see Table 40). These scenarios should be treated with caution, as they do not reflect the absolute range of uncertainty associated with the existing evidence. The results of the ERG plausible scenarios are presented in Table 41.

Table 40 ERG preferred modelling assumptions

		Company base case	ERG pessimistic	ERG optimistic
Clinical data	BSC	Jarkowski study	Jarkowski study	Pooled EGFR studies
OS	Cemiplimab Chemotherapy/ BSC	Lognormal Gompertz	Lognormal Lognormal	Gompertz Gompertz
Stopping	Cemiplimab	22 months	24 months	22 months
Effect cap	Cemiplimab	36 months	36 months	60 months
Adverse events	Cemiplimab	One off	Annual during treatment	One off
Drug costs	Cemiplimab Chemotherapy	Fixed dose 6 cycles	Weight-based 3 cycles	Fixed dose 3 cycles
Utilities		Longworth mapping	NICE TA473[57]	Longworth mapping
Health state resource use		CS Tables 35 & 37	Reduced resource use pre-progression (ERG scenario)	

Table 41 ERG modelling scenarios, deterministic (proposed cemiplimab CAA price)

	Comparator	Total cost	Total QALYs	Pairwise ICERs (cemiplimab vs comparators)
Company base case (ERG corrected)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£49,155
	BSC	[redacted]	[redacted]	£52,539
ERG optimistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£35,078
	BSC	[redacted]	[redacted]	£32,783
ERG pessimistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	£73,155
	BSC	[redacted]	[redacted]	£76,376

As expected, the results obtained from the ERG scenarios give a wide range for the ICERs comparing cemiplimab versus chemotherapy and versus BSC. For cemiplimab versus chemotherapy, the ICER ranges from £35,078 (optimistic scenario) to £73,155 (pessimistic scenario) whereas the ICER varies between £32,783 (optimistic scenario) and £76,376 (pessimistic scenario) when cemiplimab is compared with BSC. Such wide variations in results

indicate that there is not enough information to draw meaningful cost-effectiveness conclusions as to whether cemiplimab provides good value for money for the NHS at a willingness-to-pay threshold of £50,000 per QALY.

4.5 Conclusions of cost effectiveness analyses

The population in the company's economic model reflects the NICE scope and the characteristics of patients in the cemiplimab evidence base. Clinical opinion is that this population is reasonably representative of patients seen in practice, but that there is wide variation and there is no evidence from UK cohort or disease registry. Subgroup analysis is presented for locally-advanced and metastatic subgroups, as requested in the scope, but we consider that pooled evidence for the overall population is more robust than for subgroups because of the small sample sizes (n= 33 and 75 respectively).

The modelled intervention and comparators are consistent with the NICE scope and reflective of current clinical practice. The company use the best evidence for cemiplimab that is currently available, though this is limited in sample size (n=108) and follow up (median 8.92 months). However, evidence for the comparators is very weak: a retrospective cohort of only 18 patients for chemotherapy; and chemotherapy or EGFR inhibitor data used as proxies for best supportive care. Comparative effectiveness is very uncertain due to the lack of a randomised control group, and potential confounding of the observational comparisons that is not adequately adjusted for in the STC and MAIC indirect comparisons. We appreciate that the company has attempted to supplement the sparse evidence base with clinical expert opinion, using a formal expert elicitation process that appears to have been well conducted (CS Appendix M). However, we consider that this is subject to bias due to the method of expert recruitment, so do not place emphasis on the company's results that incorporate elicited expert opinion.

The company fits a wide range of functional forms to extrapolate PFS and OS and follow recommended methods to select distributions for their base case and scenarios. They appropriately restrict consideration to distributions that continue to decline, rather than those that plateau. The ERG considers the company's base case choice of PFS (Weibull) and OS (log-normal for cemiplimab and Gompertz for chemotherapy and BSC) extrapolations to be reasonable. However, it is difficult to discriminate on the basis of fit to the observed data, as the visual fit and DIC statistics are similar. The clinical plausibility of the extrapolations is also

difficult to judge because of the lack of external evidence and uncertain clinical opinion. We therefore extend the range of extrapolations tested in ERG scenario analysis and present alternative optimistic/pessimistic ERG analyses, rather than a single ERG base case.

The long-term persistence of effects for cemiplimab is unknown. The company test a good range of scenarios and their base case assumption of 3 years is relatively conservative – for example, compared with 5 years for nivolumab in NICE TA490. There is also considerable uncertainty over the optimal duration of cemiplimab treatment and whether a 'stopping rule' is appropriate or would be implemented in practice. The company assumes that patients would stop treatment at disease progression, or at a maximum of 22 months, based on the maximum limit of treatment in the phase II study protocol. However, we note that this limit has not influenced the clinical data in the model (as follow-up has not yet reached this point), and a 24-month limit is more conventional for immunotherapies. In addition, the Phase I study had a 48 week cap on treatment. We therefore extend the range of scenarios for the stopping rule: from one year to no cap on treatment duration.

The company's approach to estimating health state utilities was generally good, although the results are uncertain due to sparsity of data and the use of mapping. Base case utilities were derived from questionnaires completed by patients in the phase II study (EORTC QLQ-C30) mapped to EQ-5D-3L values using a published algorithm (Longworth et al. 2014). We consider this appropriate and agree with scenarios based on an alternative mapping algorithm (McKenzie et al. 2009) and published NICE appraisals (TA473 and TA489). However, we note an inconsistency in the model, whereby post-progression utilities declined with age (appropriately), but pre-progression utilities did not. We applied a correction for this in ERG analysis.

Other uncertainties that we consider in ERG analysis are:

- The cost and QALY impact of adverse events, which we consider to be underestimated in the company model, and is possibly biased in favour of cemiplimab (due to the omission of long-term and immune-related events).
- The company's base case estimates the cost for cemiplimab with flat dose regimen, as proposed for marketing authorisation. We test the impact of a weight-based cost, to align with the regimen for the clinical data in the model.
- Clinical experts advising the ERG suggested that the company's assumptions about the use of health care resources prior to progression are not reflective of routine NHS

practice. We therefore test a scenario with lower resource use for the pre-progression health state.

- We updated unit costs to 2018 values and corrected some errors

The company concludes from their cost-effectiveness analysis that the ICERs for cemiplimab fall below £50,000 per QALY (including the proposed CAA price discount): £43,740 per QALY compared with chemotherapy and £46,239 per QALY compared with best supportive care. Following ERG corrections, these estimates rose to: £49,155 per QALY and £52,539 respectively.

Scenario analysis showed that:

- Results are sensitive to OS extrapolations: e.g. lower ICERs when the Gompertz is used for cemiplimab and comparators; and higher ICERs with log-normal OS curves. However, results are not sensitive to changes in PFS distributions.
- The model is highly sensitive to the assumed duration of treatment and persistence of benefits, with ICERs below £50,000 per QALY when we assume only 1 year of treatment; and persistence of effects for a further year, to over £80,000 per QALY if we do not limit the duration of treatment pre-progression or the assumed duration of effects.
- Changes to the clinical data source lead to some large changes in ICERs. Excluding the phase I cemiplimab study data increases ICERs above £60,000 per QALY. The STC data and elicited estimates from experts reduce the ICER estimates.
- There is a modest increase in ICERs when the costs of cemiplimab are estimated for the weight-based regimen on which the clinical effectiveness data were based. As might be expected, this finding is sensitive to the mean weight of the population.
- Reducing health state resource use, and hence costs, causes a small reduction in estimated ICERs.
- Using a different method to estimate post-progression utilities (assuming a constant proportional reduction rather than a constant absolute reduction relative to pre-progression utilities) caused a small increase in the estimated QALY gain with cemiplimab, and hence a small reduction in the ICERs.

5 End of life

The CS argues that cemiplimab meets the NICE end-of-life criteria. Table 42 (CS Table 10) summarises their justification for reaching this conclusion.

Table 42 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In a retrospective chart review of advanced CSC patients with platinum-based chemotherapy, median OS was reported at 15.1 months. Patients who did not receive platinum chemotherapy (n=7) died by 12 months, with median OS 3.5 months. Further, the company's advisory board indicated that the survival of advanced CSCC patients in the UK would not exceed 5% at 2 years. In the economic model,[a] the mean OS for patients receiving BSC was 2.38 life years (28.56 months) using the EGFR studies, which increased to 3.63 life years (43.6 months) when data from the Jarkowski study was used. 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	[redacted] In the economic modelling, which extrapolates beyond the duration of the studies, cemiplimab is associated with a gain of [redacted][a] life years ([redacted] months) compared with chemotherapy and BSC, when costs and benefits are discounted at 3.5% per annum. With no discounting, cemiplimab was associated with a gain of [redacted][a] life years ([redacted] months) compared to chemotherapy and BSC.

[a] Based on ERG-corrected company's base case analysis

The ERG's analysis confirms that cemiplimab offers an additional extension of life, which exceeds 3 months when compared to chemotherapy or BSC. In the ERG optimistic scenario (without discounting), cemiplimab is associated with a gain of [redacted] life years ([redacted] months) compared to chemotherapy and [redacted] life years ([redacted] months) compared to BSC. In the ERG pessimistic scenario (without discounting), cemiplimab is associated with a gain of [redacted] life years

([redacted] months) compared to both chemotherapy and BSC. Whilst these observations imply that cemiplimab does meet the NICE criteria for being considered as a life-extending treatment for patients with a short life expectancy, we view that this should be treated with caution due to lack of robust clinical data for the treatments in comparison.

6 Innovation

The key points stated by the company in CS section B.2.12 (Innovation) are:

- Cemiplimab will represent a step change in the management of advanced CSCC for clinicians and patients as it will be the first and only approved systematic therapy that has demonstrated a substantial and durable tumour shrinkage.
- Cemiplimab was granted “breakthrough” designation from the FDA due to the substantial improvement on a clinically significant endpoint over available therapies.
- Cemiplimab offers a novel mechanism of action compared to currently-used chemotherapy and BSC for advanced CSCC.
- Cemiplimab offers curative potential and a possible return to normal living.

The ERG notes that:

- Validation of the clinical effectiveness and safety of cemiplimab and whether cemiplimab represents a step change in management will be dependent on the acquisition of longer-term data.
- The curative potential of cemiplimab would likely apply to a relatively small subgroup of the patients with advanced CSCC.
- There are currently no licensed systemic treatments for advanced CSCC. Although platinum-based chemotherapy may be used in some circumstances, other potential therapies including EGFR inhibitors are unlikely to be used in the NHS in England. Cemiplimab could address an unmet need for the treatment of advanced CSCC.

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8 APPENDICES

Appendix 1 ERG critique of the company's pharmacokinetic exposure analysis

Among the analyses conducted, the company compared predicted cemiplimab exposure from pharmacokinetic modelling of 505 patients who received weight-based cemiplimab for any solid tumours against observed exposure in those patients who received the fixed-dose regimen for advanced CSCC. The predicted and observed steady-state exposure concentrations show general agreement between the two dose regimens, but a limitation is that the sample size for the observed exposure group was only 16 patients (clarification question response A20). It is also unclear whether the broad population of patients with any solid tumours is an appropriate reference population for pharmacokinetic modelling in advanced CSCC given that patients might have varied on key covariates such as weight (this is not discussed). We note that there were some slight differences in the baseline characteristics between the fixed-dose and weight-based dose groups in the phase II study (section 3.1.6.3). Clinical experts advising the ERG commented that patients with advanced CSCC tend to be on the lighter end of the weight spectrum for their age, perhaps reflecting more active lifestyles (given that outdoor UV exposure is the key aetiological factor for CSCC). If weight differs systematically between patients with advanced CSCC and those with other solid tumours there could be a risk that exposure estimates from the pharmacokinetic modelling could be biased.

Appendix 2 Critical appraisal of the studies (Newcastle-Ottawa Scale)

"Quality" domain [a]		Cemiplimab phase I study		Cemiplimab phase II study		Jarkowski[8] chemotherapy study	
		CS	ERG	CS	ERG	CS	ERG
Selection	Representativeness of the exposed cohort	*	*	*	*	*	Unclear [d]
	Selection of the non-exposed cohort	NA	NA	NA	NA	NA	NA
	Ascertainment of exposure	*	*	*	*	*	Unclear [d]
	Demonstration that outcome of interest was not present at start of study	*	*	*	*	*	Unclear [d]
Comparability	Comparability of cohorts on the basis of the design or analysis	NA	NA	NA	NA	NA	NA
Outcome	Assessment of outcome	*	* [b]	*	* [b]	*	Unclear [d]
	Was follow-up long enough for outcomes to occur	*	Partly [c]	*	Partly [c]	*	*
	Adequacy of follow-up of cohorts	*	*	*	*	*	*
Comments		Median follow-up: 11.1 months		Median follow-up: 8.6 months		Follow-up not reported [e]	Median follow-up: 42.8 months [e]

Source: Based on CS Appendix Table 15 (cemiplimab studies) and CS Appendix Table 14 (comparator studies). NA: not applicable; *: appropriate

[a] For interpretation of study validity see section 3.1.4.
[b] Primary outcomes were assessed with independent central review; blinding unclear for other outcomes.
[c] Not all outcomes could be ascertained in the follow-up period, both studies are ongoing and data are immature.
[d] Study publication does not report any quality assurance methods for ensuring representativeness of the exposed cohort, ascertainment of exposure, or assessment of outcomes; ERG believes these are at high risk of bias due to the retrospective nature of the study which may have led to unrepresentative selection of participants and outcomes.
[e] Company states "Follow-up not reported; there was a high proportion of patients who dropped out of the study (~25%)". ERG cannot corroborate this, as follow-up is reported but the study publication does not mention ~25% dropout.

Appendix 3 Summary of studies of EGFR inhibitors

The EGFR inhibitor studies were all small, single-arm studies, one of which was retrospective. The main difference between these and the cemiplimab studies is the inclusion of participants with ECOG PS 2 and 3 (3%-36%). These four studies are summarised here as they serve as a proxy for BSC in the economic analysis (see section 4.4.3).

Study details	Patients: Median (range) or %	Tumour characteristics %	Prior therapy, %	ECOG PS, %	Results and author's conclusions
Gold 2018[9] USA Erlotinib 150 mg daily Single-arm, N=39	Locoregionally recurrent or metastatic CSCC not amenable to curative treatment Age: 68 (45-88) Male: 87%	Local / nodal / distant: not reported Head & neck: 79 Extremities: 13 Trunk: 8	Chemotherapy: 41 Surgery: 97 RT: 82	0: 28 1: 59 2: 13	Treatment: median 14 weeks (1 day-75 weeks) Follow-up: not reported ORR (n=29 with >4 weeks treatment): 10% OS median: 13 months (95% CI 8.4, 20.5) PFS median (n=39): 4.7 months (95% CI 3.5, 6.2) 12 month OS: 53% 12 month PFS: 14% Authors: modest response rate, expected toxicities
Picard 2017[11] France Cetuximab initial 400mg/m^2, 250 mg/m^2 weekly Retrospective, N=31	Locally advanced and surgically unresectable or metastatic CSCC Age: 86 (48-96) Male: 71%	Local: 39 Nodal: 42 Distant: 19 Head & neck: 71 Extremities: 19 Trunk: 10	Surgery alone: 29 RT alone: 3 Surgery & RT or chemotherapy: 45 None: 23	0: 16 1: 48 2: 29 3: 7	Treatment duration: not reported Follow-up: mean 19 months (1-36) ORR at week 6: 48.5% OS median: 13 months (range 1-36) PFS median: 9 months (range 0-36) 12 month OS: 52%[a] 12 month PFS: not reported Authors: treatment efficacious and warranted
Maubec 2011[10] France Cetuximab initial 400mg/m^2, 250 mg/m^2 weekly Single-arm, N=36	Locally advanced surgically unresectable or metastatic CSCC; chemo-therapy-naive	Local: 47 Nodal: 44 Distant: 8 Head & neck: 14 Extremities: 39 Trunk: 47	RT alone: 6 Surgery alone: 33 RT & surgery: 19 None: 42	0: 31 1: 47 2: 22	Treatment: up to 48 weeks, median NR Follow-up: not reported ORR at week 6 (n=36): 11%; Best ORR 28% (95% CI 14, 45) OS mean: 8.1 months (95% CI 6.9, 9.3) PFS mean: 4.1 months (95% CI 1.7, 5) 48 week OS: 52% (95% CI 34, 68)

Study details	Patients: Median (range) or %	Tumour characteristics %	Prior therapy, %	ECOG PS, %	Results and author's conclusions
	Age: 79 (32-95) Male: 58%				48 week PFS: 6%[a] Authors: shows efficacy, RCT warranted
William 2017[12] USA Gefitinib 250mg/day Single-arm, N=40	Locoregionally recurrent or metastatic CSCC not amenable to curative treatment (surgery or radiation). Age: 67 (37-95) Male: 75%	Locally advanced: 10 Recurrent: 67.5 Metastatic: 22.5 Head & neck: 80 Extremities: 15 Trunk: 5	Surgery: 88 RT: 83 Chemotherapy: 45	0: 10 1: 80 2: 10	Median treatment duration: 3.4 months (range 0.9-33.5) Follow-up: not reported ORR (n=37): 16% (95% CI 0.06, 0.32) OS: 12.9 months (95% CI 8.5, 25.0) PFS median 3.8 months (95% CI 2.2, 5.7) 12 month OS: 49%[a] 12 month PFS: 15%[a] Authors: The pre-specified target response rate was not met. Gefitinib demonstrated modest activity.

[a] Estimated from figure; RT: radiotherapy

ERG comment on validity of the EGFR inhibitor studies

The company reports a "quality assessment" for these studies in CS Appendix Table 14, based on the Newcastle-Ottawa Scale. The Newcastle-Ottawa Scale does not specifically assess validity (i.e. risk of bias) and we have not reproduced those assessments here (NB the ERG cannot verify the follow-up data for Gold et al.[9] and Picard et al.[11] as reported in CS Appendix Table 14, which do not agree with the study publications). We note that the main validity issue for all four EGFR inhibitor studies is that, in common with the cemiplimab and chemotherapy studies, they were-single-arm uncontrolled comparisons (i.e. a design that cannot unequivocally exclude selection bias and establish a cause-effect relationship). Additionally, the cetuximab study by Picard et al.[11] was retrospective and therefore at further risk of bias due to the potential for selective ascertainment of patients, exposures and outcomes. Despite these study limitations, these EGFR inhibitor studies have relative strengths when compared to the Jarkowski chemotherapy study,[8] as three of them were prospective, and all four had larger sample sizes (N=31 to 40) than in the chemotherapy study (N=18). Follow-up and treatment duration were not reported consistently in all four EGFR inhibitor studies. However, with the

possible exception of the gefitinib study by William et al.,[12] study duration appears to have been markedly longer than the currently available follow-up in the cemiplimab studies.

Appendix 4 PFS and OS extrapolations

Figure 7 PFS for cemiplimab: integrated Phase I and II studies, naive analysis (base case)
Source: CS Figure 24

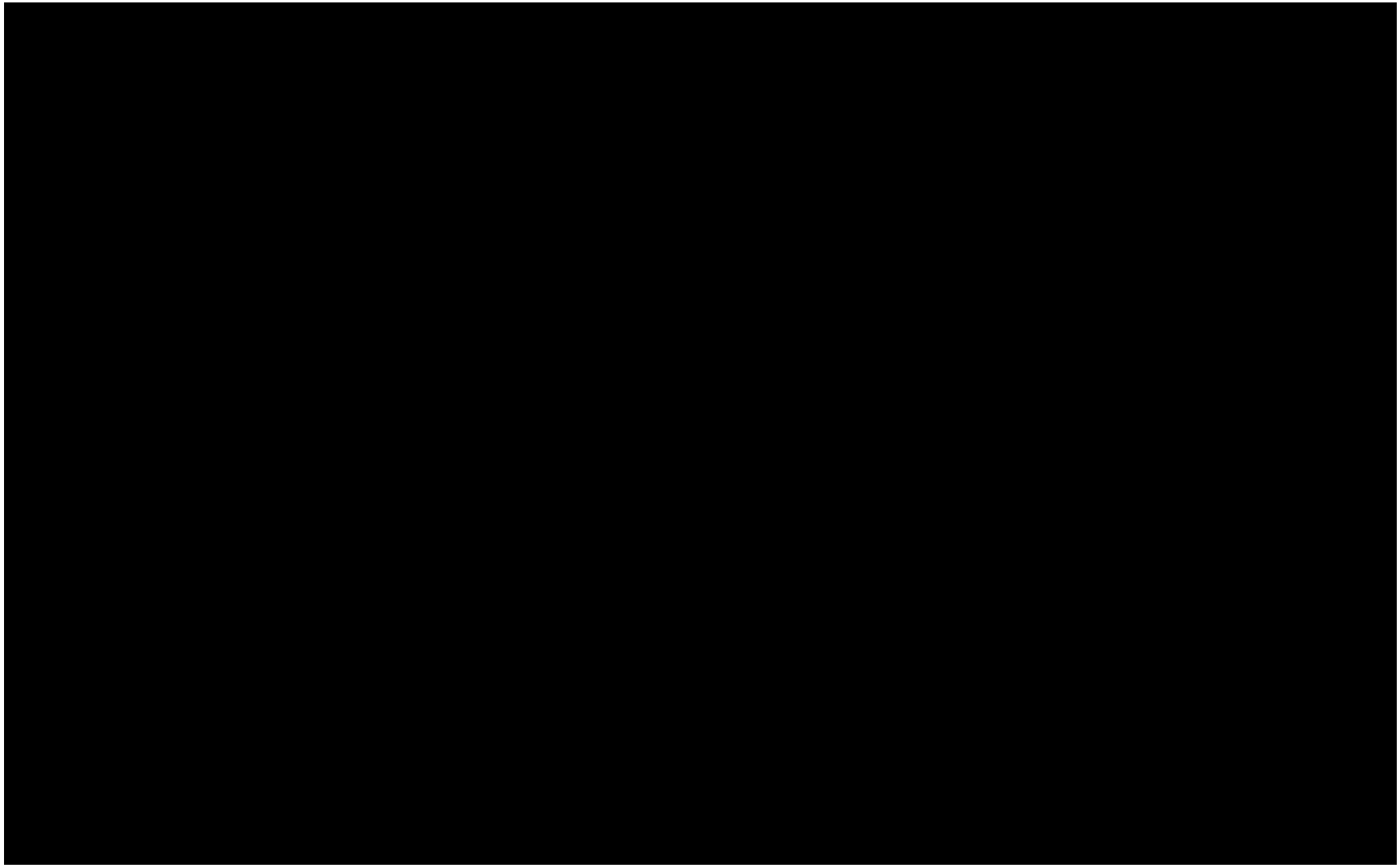

Figure 8 OS for cemiplimab: integrated Phase I and II studies, naive analysis (base case)
Source: CS Figure 25

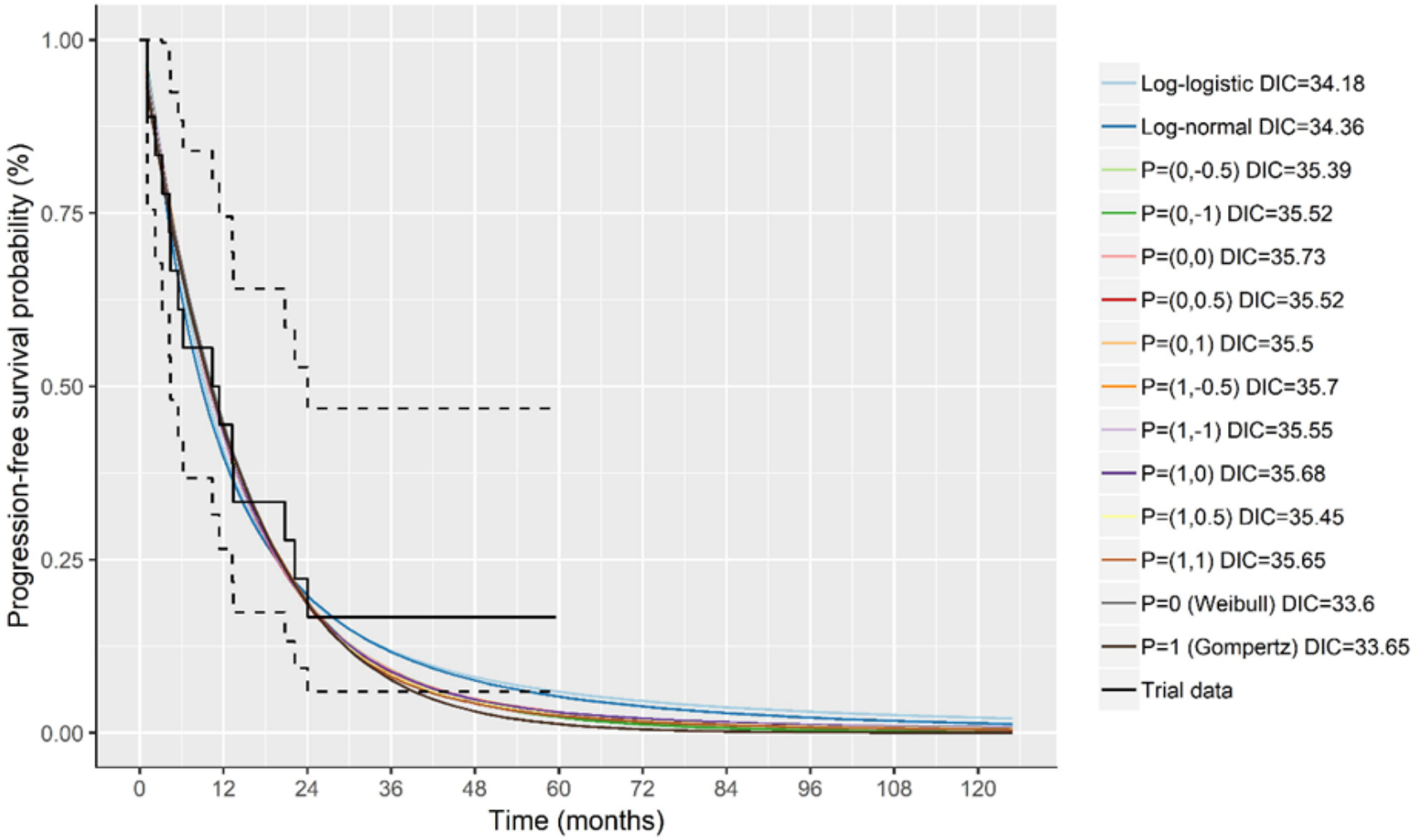

Figure 9 PFS for chemotherapy and BSC: Jarkowski cisplatin + 5-fluorouracil cohort (base case)
Source: CS Figure 29

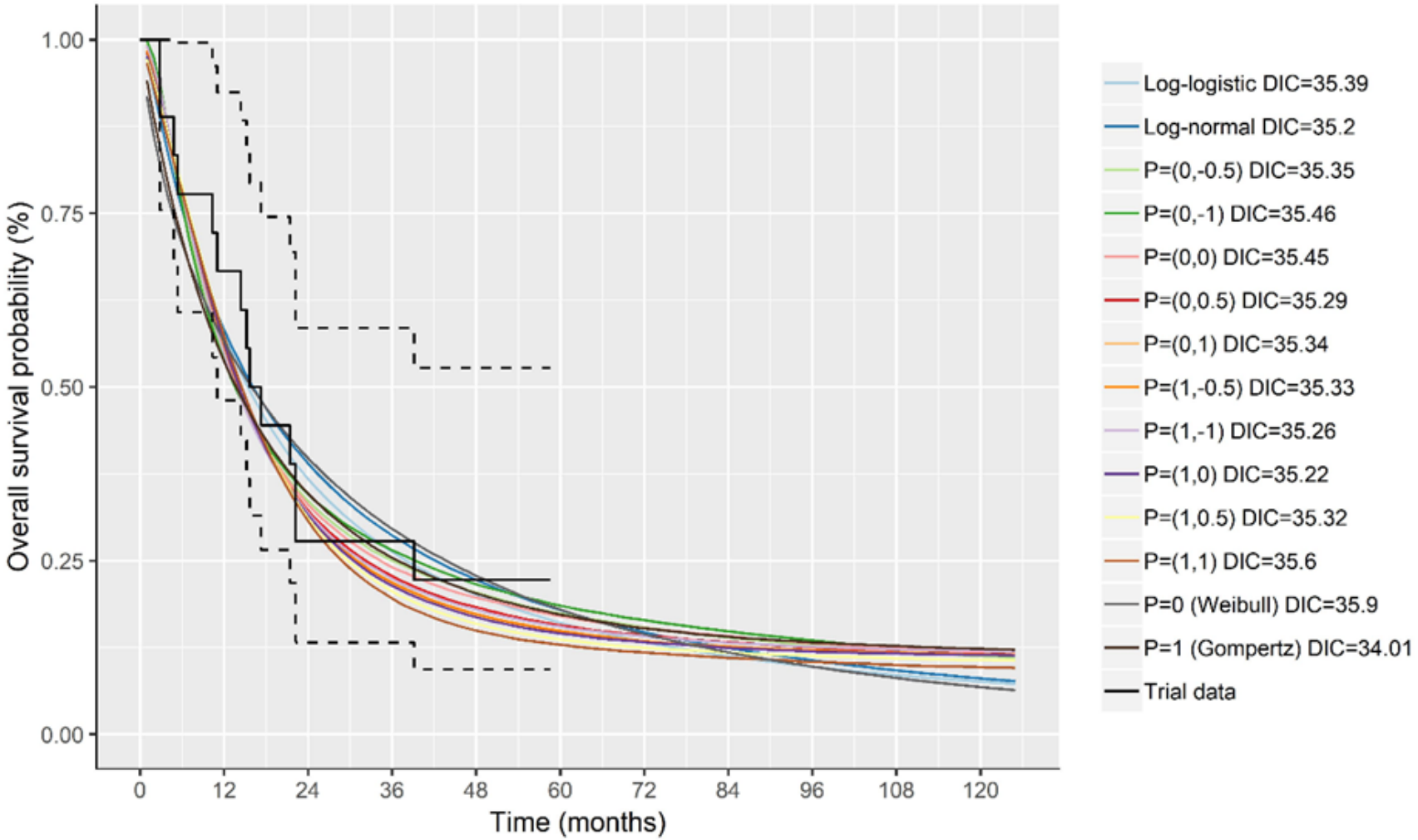

Figure 10 OS for chemotherapy and BSC: Jarkowski cisplatin + 5-Fluorouracil cohort (base case)
Source: CS Figure 30

Figure 11 PFS for BSC: Pooled EGFR inhibitor studies, fixed effects model
Source: CS Appendix Figure 59

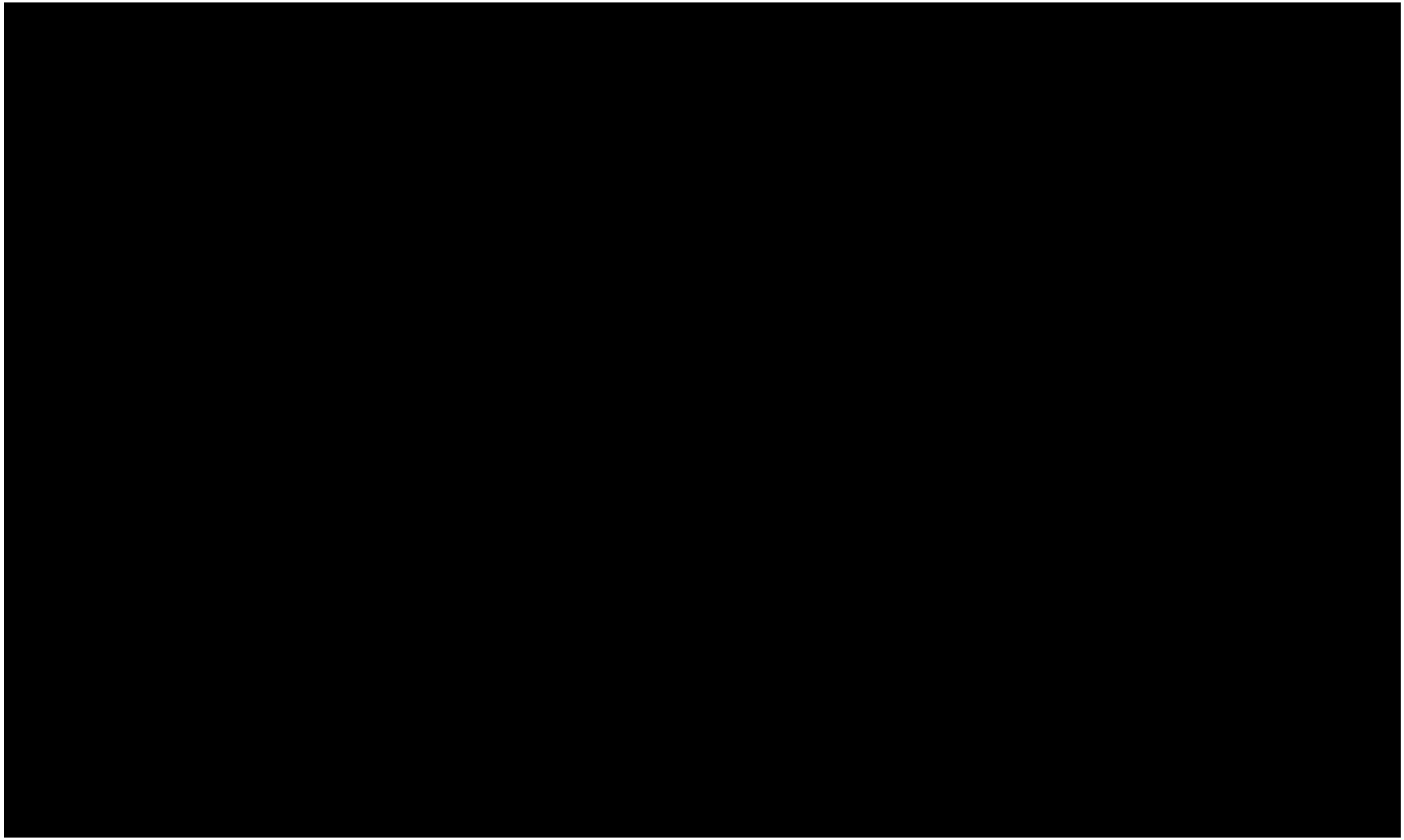

Figure 12 OS for BSC: Pooled EGFR inhibitor studies, fixed effects model
Source: CS Appendix Figure 60

Appendix 5 ERG critique of model assumptions and parameters

Table 43 ERG's preferred assumptions and scenarios

Aspect of the model	Company's base case and scenarios	Additional ERG scenarios	ERG comments
Population	Base case: overall population with advanced CSCC not suitable for curative surgery or radiotherapy, as per naïve integrated analysis of phase I and II cemiplimab studies Scenarios: metastatic and locally-advanced subgroups	None	The population and subgroups in the economic model reflect the NICE scope. Pooled evidence for the overall population is more robust than for subgroups because of the small sample sizes (n= 33 and 75 respectively for locally-advanced and metastatic).
	Patient characteristics (for overall population and subgroups, not varied in sensitivity analysis) Gender: 85% male Age, mean: 70.44 years Weight, mean (SD): Men 83.9 (15.3) kg Women 62.1 (14.8) kg BSA, mean (SD): Men 2.0 (0.2) m^2 Women 1.6 (0.2) m^2	• 75% to 95% male • 60 to 80 years	Baseline characteristics for patients in the model are based on the population in cemiplimab evidence base. Clinical opinion is that the population in the cemiplimab studies are reasonably representative, but that there is wide variation and there is no evidence from UK cohort or disease registry. We therefore explore uncertainty over the gender mix and mean age of the patient population in ERG scenario analysis. We also tested sensitivity to mean body weight and body surface area (BSA), but this did not affect cost-effectiveness in the company's base case.

Aspect of the model	Company's base case and scenarios	Additional ERG scenarios	ERG comments
Intervention	Cemiplimab costs for fixed dose (350mg per 3 weeks). Effects for weight-based regimen (3mg/kg every 2 weeks), as in phase I study and groups 1 and 2 of the phase II study	Cemiplimab costs for weight-based regimen, assuming no vial sharing, plus scenarios with weight +/- 10%	The model uses costs for a fixed dose of cemiplimab, which reflects the anticipated marketing authorisation. However, this is inconsistent with the clinical evidence that is used in the model, which relates to a weight-based regimen of cemiplimab. We test the sensitivity of the cost-effectiveness results to costs for a weight-based cemiplimab regimen.
Comparators	Chemotherapy: cisplatin + 5-fluorouracil, from Jarkowski study (retrospective cohort)[8] BSC: package of palliative treatments and care but no drug treatment	None	The modelled comparators are consistent with the NICE scope and are reflective of current clinical practice. However, the clinical evidence base for the comparators is very weak – see below.
Clinical data	Base case for cemiplimab: naïve (unadjusted) integrated analysis of phase I and II studies Scenarios: STC; phase II study data only; integrated phase I and II studies + elicited expert opinion	None	The company's base case analysis uses best current evidence for cemiplimab, but is very uncertain due to the lack of a randomised control group, and potential confounding of the observational comparisons that is not adequately adjusted for in the STC and MAIC indirect comparisons. Although apparently well conducted, the company's formal expert elicitation process is subject to bias due to the method of expert recruitment (CS Appendix M)

Aspect of the model	Company's base case and scenarios	Additional ERG scenarios	ERG comments
	Base case for chemotherapy: cisplatin +5-fluorouracil outcomes from the Jarkowski[8] study Scenarios: Jarkowski[8] study + elicited expert opinion	None	Evidence from the Jarkowski[8] study used to model outcomes for chemotherapy is very weak due to the small sample size (n=18), absence of prognostic variables required for satisfactory adjustment and retrospective data collection. However, we have not identified a better source.
	Base case for BSC: PFS and OS assumed the same as with chemotherapy (Jarkowski[8] data). Scenarios: pooled EGFR inhibitor studies[9-12]; pooled EGFR and Jarkowski[8] studies	None	There is no direct evidence for this patient population under best supportive care. The company uses chemotherapy as a proxy in their base case analysis. This is likely to be conservative: as clinical opinion is that chemotherapy may be beneficial for some patients, extending time to progression. The alternative EGFR inhibitor proxy may also be conservative, although these drugs have not been shown to be beneficial for advanced CSCC.
	PFS and OS curves are fitted independently for cemiplimab and comparators.	None	We agree with the argument that proportional hazards are unlikely to hold for OS and PFS due to different mechanisms of action for chemotherapy and immunotherapies.
PFS	PFS cemiplimab: Weibull base case (log-normal & log-logistic scenarios)	• P1=0, P2=1 • P1=0, P2=-1	The company fits a wide range of functional forms to extrapolate PFS and OS. They appropriately restrict consideration to distributions that continue to decline, rather than those that plateau, and the base case for PFS (Weibull) and OS (log-normal for cemiplimab and Gompertz for chemotherapy and BSC) appear reasonable. However, it is difficult to discriminate on the basis of fit to the observed data (as DIC
	PFS comparators: Weibull base case (log-normal & log-logistic scenarios)	None	
OS	OS cemiplimab: log-normal base case (Weibull & Gompertz scenarios)	• Log-logistic	

Aspect of the model	Company's base case and scenarios	Additional ERG scenarios	ERG comments
	OS comparators: Gompertz base case (log-normal and P1=1/P2=0 scenarios)	• Log-logistic • P1=0, P2=0	statistics are similar) or the clinical plausibility of the extrapolations (because of the lack of evidence and uncertain clinical opinion). We therefore extend the range of scenarios in ERG analysis.
Persistence of treatment effects	Base case: cemiplimab treatment effect (hazard trend) up to 36 months followed by PFS and OS hazards equal to those for chemotherapy Scenarios: continued benefit; 22-month cap; 5-year cap; constant hazard after 22 months; waning between 11 months and 5 years	None	The long-term persistence of effects for cemiplimab is currently unknown, but the company test a good range of scenarios and the base case assumption of 3 years is relatively conservative – for example, compared with 5 years for nivolumab in NICE TA490.[38]
Treatment duration	Base case: cemiplimab discontinued on progression (TTD=PFS) or maximum of 96 weeks (22 months). Scenarios: hazard ratio for TTD compared with PFS of [redacted]; and 24-month cap on treatment	• 12 month cap on treatment with 24 month effects • Continuation of treatment with 36 month cap on effects • Continuation of treatment with no cap on effects	The company's base case assumptions are reasonable, as the phase II study supported the assumption that TTD is similar to PFS and limited cemiplimab treatment to 22 months. However, this limit has not influenced the clinical data in the model (as follow-up has not yet reached this point), and a 24-month limit is more conventional for immunotherapies. In addition, the Phase I study had a 48 week cap on treatment. We therefore extend the range of scenarios tested.

Aspect of the model	Company's base case and scenarios	Additional ERG scenarios	ERG comments
	Base case: all patients assumed to complete 6 cycles of chemotherapy Scenario: mean of 3 cycles of treatment	None	The base case assumption that all patients complete the full 6 cycles of treatment is implausible. We consider that the scenario with a mean of 3 cycles of chemotherapy is more realistic
Adverse events	One-off loss of utility and costs applied in first model cycle: • [redacted] and [redacted] for cemiplimab; • [redacted] and [redacted] for chemotherapy. The model includes grade 3/4 AE rates from integrated phase I and II studies for cemiplimab and from an external source for chemotherapy (Vermorken et al).	• AE-related utility loss and cost at annual intervals during cemiplimab treatment • AE utility loss and cost for cemiplimab set equal to that for chemotherapy	We consider that the cost and utility loss due to adverse events is likely to be underestimated in the company model, and is possibly biased in favour of cemiplimab (due to the ommission of long-term and immune-related events). We therefore run additional scenario analyses to test the sensitivity of results to alternative, more conservative assumptions.

Aspect of the model	Company's base case and scenarios	Additional ERG scenarios	ERG comments
Utilities	Base case: 0.793 and 0.701 for pre and post progression respectively (Longworth mapping) Scenarios: 0.815 and 0.719 (McKenzie mapping); 0.67 and 0.52 from TA473; 0.839 and 0.757 from TA489 (locally advanced); and 0.819 and 0.639) TA489 (metastatic) Pre-progression utility fixed (0.793). Post-progression utilities decline with age from 0.703 at age 70 to 0.551 at age 100, according to published formula (Ara and Brazier 2011)	• Utility multiplier approach: PFS (0.788 to 0.611); post-progression (0.697 to 0.540)	The company's base case utilities were derived from EORTC QLQ-C30 data from the phase II study mapped to EQ-5D-3L values using a published algorithm (Longworth *et al*. 2014). We consider this appropriate and agree with scenarios based on an alternative mapping algorithm (McKenzie et al. 2009) and published NICE appraisals (TA473 and TA489). We applied a correction to the company model to adjust both pre and post-progression utility as the cohort ages, based on the Ara and Brazier formula for the general population: PFS assumed equal to general population estimates (0.788 to 0.611 for ages 70 to 100): with a fixed decrement of 0.092 on progression (0.696 to 0.519). The ERG scenario uses a utility multiplier (0.884) to estimate post-progression utilities relative to PFS values.
Costs	Monthly drug acquisition costs for fixed dose cemiplimab ([redacted] with proposed CAA discount; [redacted] at list price); £41 per month for cisplatin and 5-fluorouracil (with wastage assuming no vial sharing)	• Weight-based regimen for cemiplimab ([redacted] with proposed CAA discount; [redacted] at list price) • As above + 10% mean population weight	The company's base case estimates the cost for cemiplimab with flat dose regimen, as proposed for marketing authorisation. We test the impact of a weight-based cost, to align with the regimen for the clinical data in the model.

Aspect of the model	Company's base case and scenarios	Additional ERG scenarios	ERG comments
	Health state resource use for pre and post progression based on expert opinion (CS Tables 35 and 37). Same values across treatment arms (except higher rate of palliative surgery assumed after cemiplimlimab).	• Reduced resource use pre-progression: fewer consultations with oncologist and nurses; fewer blood tests; and less use of palliative radiotherapy	Clinical experts advising the ERG suggested that the company's assumptions about the use of health care resources prior to progression are not reflective of routine NHS practice. We therefore test a scenario with lower resource use for the pre-progression health state.
	Unit costs for drug administration and palliative treatment and care from 2016/17 NHS Reference Costs[40] and 2017 PSSRU. End of life care cost from Round et al. 2015.	None	ERG updated unit costs to 2018 values[38, 68, 69] and corrected some errors
Discount rates	Base case: 3.5% per year for costs and health effects Scenarios: 0%, 1.5% & 6%	None	
Time horizon	Base case: 30 years Scenarios: 5, 10 & 20 years	None	

Appendix 6 ERG analysis results based on the cemiplimab list price

(a) Base case, deterministic analysis

Table 44 Cost effectiveness: ERG corrected company base case, deterministic (list price for cemiplimab)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cemiplimab	[redacted]	[redacted]			

(b) Base case, probabilistic analysis

Table 45 Cost effectiveness: ERG corrected company base case, probabilistic (list price for cemiplimab)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cemiplimab	[redacted]	[redacted]			

(c) One-way deterministic sensitivity analyses: tornado plots

Figure 13 Tornado plot for cemiplimab vs chemotherapy: ERG-corrected company base case, cemiplimab list price

Figure 14 Tornado plot for cemiplimab vs BSC: ERG-corrected company base case, cemiplimab list price

(d) Scenario analyses

Table 46 ERG-corrected company scenario analyses, cemiplimab list price

Base case input	Scenario	ICER versus chemotherapy	ICER versus BSC
Base case results		[redacted]	[redacted]
Comparative efficacy: Naïve	STC	[redacted]	[redacted]
22 month stopping rule	24 month stopping rule	[redacted]	[redacted]
Assumption regarding continued treatment benefit following the 22-month treatment cap: 3-year cap	Continued benefit	[redacted]	[redacted]
	22-month cap	[redacted]	[redacted]
	5-year cap	[redacted]	[redacted]
	Constant hazard after 22 months	[redacted]	[redacted]
	Waning effect between 22 months to 5 years	[redacted]	[redacted]
Integrated analysis of phase I and phase II trials	Phase II study	[redacted]	[redacted]
Alternative curve fits for cemiplimab: OS	Gompertz	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]
Alternative curve fits for cemiplimab: PFS	Lognormal	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]
Alternative curve fits for chemotherapy: OS	Lognormal	[redacted]	[redacted]
	Second-order fractional polynomial P1=1, P2=0	[redacted]	[redacted]
Alternative curve fits for chemotherapy: PFS	Lognormal	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]
Cemiplimab time on treatment equal to PFS	Adjustment for time on treatment	[redacted]	[redacted]
Chemotherapy: 6 treatment cycles	3 treatment cycles	[redacted]	[redacted]
Utilities: EQ-5D mapped from Phase II EORTC QLQ C-30, Longworth algorithm	McKenzie algorithm	[redacted]	[redacted]
	SCCHN (TA473)	[redacted]	[redacted]
	ERIVANCE trial laBCC	[redacted]	[redacted]
	ERIVANCE trial mBCC	[redacted]	[redacted]
Population: Pooled	Locally advanced	[redacted]	[redacted]
	Metastatic	[redacted]	[redacted]
Time Horizon: 30 years	20 years	[redacted]	[redacted]
	10 years	[redacted]	[redacted]
	5 years	[redacted]	[redacted]
Discount rate: 3.5% for costs + QALYs	0%	[redacted]	[redacted]
	6%	[redacted]	[redacted]
	1.5%	[redacted]	[redacted]
Efficacy of BSC: equal to chemotherapy	Pooled EGFR studies	N/A	[redacted]
	All studies pooled	N/A	[redacted]

Base case input	Scenario	ICER versus chemotherapy	ICER versus BSC
Long term extrapolations of cemiplimab, chemotherapy and BSC: based on the integrated analysis of cemiplimab studies and Jarkowski study	Based on the cemiplimab phase II study + experts' elicitation and Jarkowski study + experts' elicitation	[redacted]	[redacted]

(e) ERG additional scenario analyses

Table 47 ERG scenarios: ERG-corrected company base case, deterministic, cemiplimab list price

Scenario	Comparator	Total costs	Total QALYs	Pairwise ICERs (cemiplimab vs comparators)
Company base case (ERG corrected)	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
Patient characteristics				
Gender: 75% male	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
Gender: 95% male	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
Mean age: 60 years	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
Mean age: 80 years	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
Weight-based cost for cemiplimab				
Costs for weight-based regimen	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
Costs for weight-based regimen with higher mean patient weight (+10%)	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
PFS extrapolations				
Cemiplimab: p1=0; p2=1	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]

Scenario	Comparator	Total costs	Total QALYs	Pairwise ICERs (cemiplimab vs comparators)
Cemiplimab: p1=0; p2=-1	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
OS extrapolations				
Cemiplimab: log-logistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Chemotherapy: p1=0; p2=0	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Chemotherapy: log-logistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Treatment duration: cemiplimab				
Treatment cap at 1 year with effects for 2 years	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
No treatment cap with effects for 3 years	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
No treatment cap or limit on duration of effects	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Utilities				
Multiplier approach to estimate post-progression utilities	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Adverse events for cemiplimab				
Annual recurrence of AE cost and QALY loss for duration of treatment effects (3 years)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
As above + equal AE QALY loss and costs for cemiplimab and chemotherapy	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
Resource use				
Reduced resource use before progression (ERG clinical scenario)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]

(f) ERG preferred modelling assumptions

Table 48 ERG preferred modelling assumptions

		Company base case	ERG pessimistic	ERG optimistic
Clinical data	BSC	Jarkowski study	Jarkowski study	Pooled EGFR studies
OS	Cemiplimab Chemo/ BSC	Lognormal Gompertz	Lognormal Lognormal	Gompertz Gompertz
Stopping	Cemiplimab	22 month	24 month	22 month
Effect cap	Cemiplimab	36 month	36 month	60 month
AEs	Cemiplimab	One off	Annual during treatment	One off
Drug costs	Cemiplimab Chemotherapy	Fixed dose 6 cycles	Weight-based 3 cycles	Fixed dose 3 cycles
Utilities		Longworth mapping	NICE TA473	Longworth mapping
Health state resource use		CS Tables 35 & 37	Reduced resource use pre-progression (ERG scenario)	

(g) Comparison of company base case with ERG 'optimistic' and 'pessimistic' scenarios

Table 49 ERG deterministic modelling scenarios, cemiplimab list price

	Comparator	Total cost	Total QALYs	Pairwise ICERs (cemiplimab vs comparators)
Company base case (ERG corrected)	Cemiplimab Chemotherapy BSC	[redacted] [redacted] [redacted]	[redacted] [redacted] [redacted]	 [redacted] [redacted]
ERG optimistic	Cemiplimab Chemotherapy BSC	[redacted] [redacted] [redacted]	[redacted] [redacted] [redacted]	 [redacted] [redacted]
ERG pessimistic	Cemiplimab Chemotherapy BSC	[redacted] [redacted] [redacted]	[redacted] [redacted] [redacted]	 [redacted] [redacted]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Cemiplimab for treating cutaneous squamous cell carcinoma [ID1367]

You are asked to check the ERG report from SHTAC to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 22 January 2019** using the below proforma 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.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Use of term "no curative local therapy"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 17, 18, 20 & 27, when referring to the patient population under consideration for this submission, the ERG refers to *"people with metastatic or locally advanced CSCC in whom there is no curative local therapy."* However, Sanofi believe that the term "no curative local therapy" is not specific enough in the context of the patient population under consideration and our expected license indication from the EMA.	It is proposed that the population is described as *"*People with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiotherapy.*"*	The updated wording of our anticipated indication in line with the population under consideration for this submission is as follows: Cemiplimab as monotherapy is indicated for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.	Thank you for highlighting the potential for misinterpretation here. We have adjusted the text on pages 17-18, 20 & 37 as suggested (NB correction made on page 37, as the reference to page 27 appears to be incorrect).

Issue 2 Description and critique of the approach to validity assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28 Section 3.1.4 Description and critique of the approach to validity assessment "The company also assessed the quality of four EGFR inhibitor studies[9-12] (CS Appendix Table 14). These studies were not included in the company's systematic review but were used as a proxy for BSC	It is proposed that the statement be revised as follows: "The company also assessed the quality of four EGFR inhibitor studies[9-12] (CS Appendix Table 14). These studies were included in the company's systematic review but **were not deemed relevant to the decision**	The statement in section 3.1.4 is not accurate as the four EGFR inhibitor studies matched the study eligibility criteria of the systematic review and were indeed included in the evidence base. However, EGFR inhibitors were not deemed relevant to the	Thank you for highlighting the potential for misinterpretation here. The only change necessary is to change "systematic review" to "indirect treatment comparison" and we have done this on page 28.

in the economic analysis (as explained below in section 4.3.4.4)."	**problem in the clinical effectiveness analysis. However, they** were used as a proxy for BSC in the economic analysis (as explained below in section 4.3.4.4)."	decision problem in the clinical effectiveness analysis. For further details, please see section B.2.1 and Figure 4 of the CS document.	

Issue 3 Identification and analysis of prognostic factors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 Section 3.1.7.3 Identification and analysis of prognostic factors The company did not attempt to estimate the extent of systematic error due to unaccounted for covariates using out-of-sample or in-sample methods as proposed in the NICE DSU guidance on methods for population-adjusted indirect comparisons.[1]	It is proposed that the statement be revised as follows: "The company **were unable** to estimate the extent of systematic error due to unaccounted for covariates using out-of-sample or in-sample methods as proposed in the NICE DSU guidance on methods for population-adjusted indirect comparisons **given the lack of available data**.[1]"	The proposed in-sample methods would have required splitting the IPD for cemiplimab into equal size sets for the purposes of cross validation. Given that the sample of cemiplimab patients was already small combined with the method tending to underestimate bias, it was felt that this would not provide meaningful information on the acknowledged uncertainty of the ITC estimates. The proposed out-of-sample methods in the DSU guidance suggest that random-effects modelling should be conducted on a set of external studies to assess the between study variance. As no other studies of chemotherapy were identified it was not possible to apply this approach.	The CS does not report any assessment of the extent of systematic error due to unaccounted for covariates, or provide an explanation of why this was not feasible. However, we agree that the ERG's wording might appear harsh given the data limitations. We have adjusted the text on page 43 to reflect this.

Issue 4 Academic in confidence information regarding the effect of cemiplimab on HRQoL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 32, 48 and 49 Sections 3.1.5.3. and 3.3.3. Confidential information on the effect of cemiplimab on HRQoL is not marked as academic in confidence.	It is proposed that the relevant paragraphs are revised as follows: "The CS presents relatively few results from the EORCT QLQ-C30 but does refer to a [redacted] We note that the study by Raman et al.[20] (which reported MCID=9.4 for improvement in pain) was specifically on a population with bone cancer, and it is unclear how relevant this is to patients with advanced CSCC (possibly more relevant to those with bone metastases than those without). [redacted]" "HRQoL data were not collected in the phase I study. In the phase II study, the CS states that [redacted]	Wording contains confidential information on unpublished data from the Phase II EMPOWER-CSCC 1 study.	Thank you for identifying the missing AIC markup. ERG report page 32: According to CS section B.2.6.4.1 the only AIC information in the following sentence is the reference to the pain symptom subscale. We have marked this as confidential, as follows: "The CS presents relatively few results from the EORCT QLQ-C30 but does refer to a potentially clinically meaningful change [redacted] (CS section B.2.6.4.1), citing Raman et al.[20] as the benchmark for what the company considered may be a clinically meaningful change." ERG report page 32 (continued): We agree that some of the following text should be marked AIC, but not the whole sentence. We have added AIC highlighting as follows: "In addition, the baseline pain score in the phase II study [redacted] was [redacted] than in Raman et al. (mean 69.7)[20] and it is uncertain

	[redacted]." **"ERG conclusion:** The EORTC QLQ-C30 scale indicated [redacted] while patients in the phase II study were receiving cemiplimab. However, the clinical significance of this is uncertain."		whether the reported MCID has the same clinical relevance at this baseline." ERG report page 48: We have added AIC highlighting as follows (i.e. as suggested, apart from the final part of the paragraph in brackets): "HRQoL data were not collected in the phase I study. In the phase II study, the CS states that [redacted] (the clinical relevance of EORTC QLQ-30 scores is considered above in section 3.1.5.3)." ERG report page 49: We have added AIC highlighting as suggested: **"ERG conclusion:** The EORTC QLQ-C30 scale indicated [redacted] while patients in the phase II study were receiving cemiplimab. However, the clinical significance of this is uncertain."

Issue 5 Summary of the ITC approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44 Section 3.1.7.5 Summary of the ITC approach: MAIC and STC methods of ITC further reduce the already small effective sample size.	It is proposed that the statement be revised as follows: "MAIC methods of ITC further reduce the already small effective sample size."	STC methods do not reduce the effective sample size in the comparator trial, though they do introduce variation as a result of the estimation procedure. This variation is a function of the variation observed in the IPD that was used to generate the regression models, and is therefore based on a reasonably sized sample. None of this, however, can obviate the problem of using a small sample.	Thank you for highlighting this error, which we have now corrected on page 44 and also in the summary (page 13).

Issue 6 Academic in confidence information regarding the subgroup analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49 Section 3.3.4 Confidential information from the subgroup analysis is not marked as academic in confidence.	It is proposed that the relevant section is revised as follows: "Median follow-up for the mCSCC group was [redacted] in the phase I study and [redacted] in the phase II study. For the laCSCC group, median follow-up was [redacted] in the phase I study and [redacted]	Wording contains confidential information on unpublished data from the Phase I and the Phase II EMPOWER-CSCC 1 studies.	Thank you for identifying the missing AIC markup. We have added AIC highlighting on page 49 as suggested.

	[redacted] in the phase II study (clarification question response A4)."		

Issue 7 Comparison of adverse events for other immune checkpoint inhibitors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 3.3.6.4 (page 58), the ERG report included a network meta-analysis by Xu et al. (BMJ, 2018, reference 34) entitled "Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis." The ERG uses this paper to compare pooled grade 3 or 4 adverse events (AEs) for immune checkpoint inhibitors with that of grade ≥3 events for cemiplimab from the safety analysis set.	It is proposed that the current text below: "The pooled incidence of grade 3 or 4 adverse events were: 14.1% and 19.8% respectively for the PD-1 inhibitors nivolumab and pembrolizumab; 15.1% for the PD-L1 inhibitor atezolizumab; and 28.6% for the CTLA-4 inhibitor ipilimumab. These are [redacted] with at least one Grade ≥3 event seen in the safety analysis set of the cemiplimab studies. The incidence of Grade 3 or 4 events in the analysis by Xu et al. was higher with one other immunotherapy drug, tremelimumab, a CTLA-4 inhibitor (52.3%), but this is based on one study only.[34]" is revised as: "The pooled incidence of treatment related grade 3 or 4 adverse events were: 14.1% and 19.8% respectively for the PD-1 inhibitors nivolumab and pembrolizumab. This compares with [redacted] and [redacted] patients	The comparison is inappropriate as the network analysis by Xu et al is referring to "treatment related adverse events," whilst the cemiplimab reported results quoted are referring to treatment emergent adverse events (TEAEs). A more appropriate comparison for cemiplimab would be the % patients who had grade ≥ 3 immune related adverse events (irAEs). This is reported in section 3.3.6.2 (page 55), where [redacted] of patients had grade ≥3 irAEs in the cemiplimab safety analysis and [redacted] patients in the all patient safety (pool 3). (reference: Sanofi Clinical Study Report – 2.5 Clinical Overview, page 56) It should be noted that irAEs does not include infusion-related reactions (IRR), of which there were [redacted] grade ≥ 3 IRR associated with cemiplimab in the	Thank you for identifying this discrepancy. We have reworded the text in section 3.3.6.4 (page 58) as follows to address this: "The pooled incidence of grade 3 or 4 treatment related adverse events were: 14.1% and 19.8% respectively for the PD-1 inhibitors nivolumab and pembrolizumab; and 15.1% for the PD-L1 inhibitor atezolizumab. This compares with [redacted] having at least one Grade ≥3 treatment related adverse event (i.e. irAE) in the safety analysis set of the cemiplimab studies. We note that irAE reported in the cemiplimab studies do not include infusion related reactions, of which there were [redacted] in the Pool 3 safety analysis ([redacted] in the integrated analysis). An important limitation of these comparisons is that the studies included in the meta-analysis by Xu et al.[34] were heterogeneous in terms of the

	having at least one Grade ≥3 irAE seen respectively in the safety analysis set and the all patient safety set (pool 3) of the cemiplimab studies. It should be noted that irAEs does not include infusion-related reactions (IRR), of which there were [redacted] grade ≥ 3 IRR associated with cemiplimab in the all patient safety data set (pool 3)."	all patient safety data set (pool 3).	cancer types and length of follow-up, and Xu et al.[34] did not report the age of participants included in their analysis or the comorbidities experienced by patients."

Issue 8 Stopping rule

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 Section 4.3.5.1 Treatment duration: Cemiplimab: "We therefore extended the range of assumptions about stopping rules and persistence of treatment benefits for cemiplimab in ERG scenario analyses, including; […] • no stopping rule, with a 36-month limit on duration of relative treatment effects;" Page 106	Reconsider whether this scenario analysis is appropriate for inclusion in the report.	This scenario may not be plausible, as it implies patients who are still receiving treatment following 36 months can no longer receive benefit of treatment.	Not a factual inaccuracy. No change made. We agree that this scenario is very conservative, but we included it to illustrate the extent of uncertainty over the relative treatment effects due to the paucity of comparative data.

Table ERG additional scenarios: Treatment stopping and persistence of effects - No stopping rule, 3-year effects			

Issue 9 Data sources

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 Section 4.3.4.1. Data sources: "This excludes those patients in the phase II study allocated to a fixed dose and those with follow-up less than 9 months from baseline."	It is proposed that the text is revised as follows: "This excludes those patients in the phase II study allocated to a fixed dose and those with follow-up less than 9 months from baseline **due to the inadequate follow-up and the lack of centrally reviewed data based on the October 2017 data cut at the time of the submission.**"	Amendment proposed to provide justification for the exclusion of the aforementioned groups of patients from the available evidence at the time of the submission.	We agree that it is helpful to remind the reader of the reason for this exclusion, but would rather not introduce additional text at this point. Instead, we have inserted a cross-reference on page 73 to the section in the ERG report where this point is introduced (3.1.3).

Issue 10 Academic in confidence information regarding the progression free survival

Description of problem	Description of proposed amendment	Justification for amendment
Pages 78 and 79 Section 4.3.4.6.1. Confidential information on the progression free survival associated	It is proposed that relevant sections are revised as follows: "This leaves 6 distributions, with 5-year PFS estimates between [redacted]."	Contains confidential information on unpublished analyses for cemiplimab. **ERG response**

with cemiplimab is not marked as academic in confidence.	<table><tr><th rowspan="2">Distribution</th><th rowspan="2">Company analysis</th><th rowspan="2">ERG extra scenarios</th><th rowspan="2">DIC</th><th colspan="4">Not capped by assumed duration of treatment effect or survival estimates</th></tr><tr><th>3 year</th><th>5 year</th><th>10 year</th><th>20 year</th></tr><tr><td colspan="8">Cemiplimab (naive integrated analysis of Phase I and II studies)</td></tr><tr><td>P1=0, P2=1</td><td></td><td>Scenario</td><td>57.03</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>P1=1, P2=0</td><td></td><td></td><td>56.82</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Weibull</td><td>Base case</td><td></td><td>54.85</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Log-logistic</td><td>Scenario</td><td></td><td>55.38</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Log-normal</td><td>Scenario</td><td></td><td>53.70</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>P1=0, P2=-1</td><td></td><td>Scenario</td><td>55.23</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>	Thank you for pointing out this omission. We have added AIC marking on pages 78 and 79 as requested.

Issue 11 Academic in confidence information regarding the overall survival

Description of problem	Description of proposed amendment	Justification for amendment
Pages 79 and 80 Section 4.3.4.6.2. Confidential information on the overall survival associated with cemiplimab is not marked as academic in confidence.	It is proposed that relevant sections are revised as follows: "For cemiplimab, we report four distributions, with 5-year survival ranging from [redacted]." <table><tr><th rowspan="2">Distribution</th><th rowspan="2">Company analysis</th><th rowspan="2">ERG extra scenarios</th><th rowspan="2">DIC</th><th colspan="4">Not capped by assumed duration of treatment effect</th></tr><tr><th>3 year</th><th>5 year</th><th>10 year</th><th>20 year</th></tr><tr><td colspan="8">Cemiplimab (naive integrated analysis of phase I and II studies)</td></tr><tr><td>Log-logistic</td><td></td><td>Scenario</td><td>32.75</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Weibull</td><td>Scenario</td><td></td><td>32.66</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>	Contains confidential information on unpublished analyses for cemiplimab. **ERG response** We have added AIC marking to pages 79 and 80 as requested.

Log-normal	Base case		31.51	[redacted]	[redacted]	[redacted]	[redacted]	
Gompertz	Scenario		31.76	[redacted]	[redacted]	[redacted]	[redacted]	

Issue 12 Academic in confidence information regarding cemiplimab

Description of problem	Description of proposed amendment	Justification for amendment
Pages 78 and 79 Section 4.3.4.8. Confidential information on the overall survival and progression free survival associated with cemiplimab is not marked as academic in confidence.	It is proposed that relevant sections are revised as follows: "The extrapolations used in the company's base case analysis are shown in Figure 2 and Figure 3 below, including the 3-year cap on relative effects, which reduces the 5-year estimates for cemiplimab to [redacted]"	Contains confidential information on unpublished analyses for cemiplimab. **ERG response** We have added AIC marking as requested: note this issue relates to pages 81 and 82 (not pages 78 or 79).

	 **Figure 1 PFS extrapolations: company base case**  **Figure 3 OS extrapolations: company base case**	

Issue 13 Health related quality of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 89 Section 4.3.7. Health related quality of life: "However, the company notes that the resulting general population utility for the cohort (0.788) is greater than the mapped estimate for the pre-progression state (0.793)"	Suggest following revision to the text: However, the company notes that the resulting general population utility for the cohort **(0.786**) is **less** than the mapped estimate for the pre-progression state (0.793)**. Using the approach suggested by Ara and Brazier (2011) to estimate age-related utility decrement for the pre-progression state provided a multiplier, which suggested utility increased with age. The company omitted the age-adjustment for pre-progression as increasing utility with age is clinically implausible.**	The general population utility given baseline starting age and gender distribution of patients in the integrated Phase 1 (n=26) and EMPOWER CSCC 1 (n=82 SAF data set) populations, is 0.786. The current text misrepresents why the utility remained constant, clarification is requested to highlight that application of the multiplier would result in an implausible decrement.	Thank you for pointing out our error in reporting that the general population utility is **greater** than the mapped study estimate at baseline. We have corrected this to "**less** than" on page 89. We have not changed the cited value for the baseline general population utility (**0.788**). This is because, although the value from the Ara and Brazier equation is 0.786 for an initial age of 70.44 years, the Markov trace calculations in the model actually use a rounded baseline age of 70 years, for which the utility is 0.788. See for example, the 'ROUNDOWN' formula in columns BQ and BS of the Arm 1 sheet. We have also not added the suggested additional text on page 89, as this does not address a factual inaccuracy and we do not consider that it would add to the clarity of our report. The NICE DSU Technical Support Document 12 by Ara and Wailoo gives practical

			advice on use of health state utility values in models, and takes account of the Ara and Brazier 2011 results. In particular, TSD 12 does not endorse the use of a single fixed utility, irrespective of age: "When extrapolating beyond the duration of the clinical trial, for example when using a lifetime horizon, analysts should endeavour to supplement HSUVs used to account for potential changes due to factors such as age and increasing numbers of comorbidities, for example by using data from the general population as the baseline". (TSD 12 5.1.1)
Page 89 Section 4.3.7. Health related quality of life: "We applied an alternative approach in ERG corrections [..] applying a utility decrement (0.793 – 0.701 = 0.092 in the base case) to estimate post-progression utility."	Suggest updating the approach used by the ERG to be consistent with the approach used in previous submission based on the paper by Ara and Brazier.[2]	The ERG have updated the age-related utility decrement for the post-progression utility from 0.089 to 0.092, estimated as the difference between the pre-progression and post-progression utilities, which is then subtracted from the utility for the general population for a given age. In the application of the age-related utility decrements in TA522[3], the ERG noted that the age-related utility decrement should be applied multiplicatively rather than	Not a factual inaccuracy. We consider that the ERG method of utility estimation is consistent with TSD 12 and gives a more plausible interpretation of the available data than the company's approach. There are three key changes that we applied in our revisions to the utility calculations: 1) We set the baseline utility for the progression-free health state equal to the utility for the general

		subtracted. The multiplicative model used in the CS assumes a proportional effect, combining the health state of interest (i.e. post-progression) with a given the baseline utility of the cohort. The multiplier for post-progression (multiplier=0.892) represents the utility of the health state (i.e. utility=0.701 for post-progression) divided by the baseline utility of patients given the starting age and gender of the utility source (i.e. baseline utility=0.786 based on age of 70.4 years; 85.2% male from EMPOWER-CSCC 1). By subtracting the difference between the pre-progression and post-progression utilities from the baseline utility of the general population, the ERG have estimated and applied a baseline post-progression utility of 0.696 in the model. Firstly, this approach does not accurately reflect the EMPOWER-CSCC 1 data, where the reported baseline utility for post-progression is 0.701 (applying the multiplier gives a baseline utility of 0.703). It also results in excessive depreciation in utilities post-progression due to age.	population from the Ara and Brazier formula (0.788). This is because we consider it implausible that baseline utility is better for people with non-progressed advanced CSCC than for other people of the same age. We understand that the baseline mapped utility from the phase II study data was better than the general population estimate, but there are a number of reasons for believing that the study estimates may be subject to error or bias: the mapping sample was small (n=62); there is additional uncertainty due to the mapping; and study participants do tend to be healthier than real-world populations (e.g. because of exclusion criteria related to comorbidities). 2) We do not believe that having non-progressed advanced CSCC can be protective against age-related onset of comorbidities, hence it is not credible to assume constant utility for the pre-progression health state. In

			the absence of better evidence, we assume that utility for the PF health state declines with age at the same rate as in the general population, as reflected in the Ara and Brazier formula (from 0.788 at age 70 to 0.611 at age 100). 3) We applied a fixed utility decrement (0.092) for progression based on the difference in mapped utilities pre vs. post progression from the phase II study data. Ara and Brazier 2011 concluded that "decrements on HRQoL associated with health conditions are not constant across age. Some conditions showed an increasing trend and others showed a decreasing trend" (p543). However, in the absence of evidence relating to how the decrement for CSCC progression changes with age, we think it reasonable to assume that the decrement is constant. We chose to use a decrement to model utilities for the post-progression (PP) state relative to

			(age-adjusted) PF utilities, although we could have used a multiplier approach. Both methods are common in NICE appraisals (see for example, Pennington et al 2018, nicedsu.org.uk/methods-development/eq-5d-5l/). It is not clear from a theoretical or clinical standpoint which approach is more appropriate for modelling the reduction in utility associated with CSCC progression: a constant absolute decrement; or a constant proportional decrement. TSD 12 recommends a multiplicative approach for combined (co-morbid) health conditions (TSD 12 5.2.1), but this is not relevant for the cemiplimab model. However, for clarity, we have added an ERG scenario to show the impact of using a multiplicative rather than decrement approach to estimate utilities for post-progression relative to those for pre-progression (ERG report pages 15, 89, 105, 107, 108, 113, 137, 144). This scenario gives slightly higher utilities for the post-progression state (from 0.697 at age 70 to 0.540 at age 100)

			compared with the decrement approach (0.696 to 0.519). This does not have a substantive impact, although the ICERs are slightly lower (a reduction of about £300).
Page 89 Section 4.3.7. Health related quality of life: "The results lack face validity, because the pre-progression utility is higher than estimates for the general population (adjusted for age and gender)."	Suggest removing text.	Cancer patients have often been reported to value health states higher than the general population, and patients self-reported EQ-5D scores resulting in higher utilities than that of the general population have been observed in previous NICE submissions.[4-9] On Page 89 the ERG note "Clinical experts advising the ERG suggested that basal cell carcinoma and Merkel cell carcinoma are the most comparable skin cancers to the target population." The general population utility for baseline age in the NICE TA489 submission is 0.822, lower than the utility provided for the pre-progression utility for the laBCC population (0.839). These findings suggest the pre-progression utility for cemiplimab does not lack face-validity.	Not a factual inaccuracy (see discussion above). No change made to ERG report.

Issue 14 Model validation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 93 Section 4.3.9. Model validation: "The company cross-validated the economic model by comparing the output with results reported in the literature, although no details on these comparisons are reported in the submission."	Suggest following revision to the text: "The company cross-validated the economic model by comparing the output with **clinical outcomes** reported in the literature."	Revision to text suggested for clarity, as in the CS a comparison was made between clinical outcomes and relevant publications in the literature (Table 47 and Table 48 in the CS).	This statement relates to the paragraph on 'cross-validation' against other models on page 177 of the CS (section B.3.10.1). We referred to the internal validation of clinical outcomes from the model against sources for model inputs (CS Tables 47 and 48) in the preceding bullet points on page 93. We revised the text on page 93 of the ERG report to: "The company stated that they had cross-validated the economic model by comparing the output with results of other models reported in the literature (CS section B.3.10.1)"

Issue 15 Scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 Section 4.3.10.4. Scenario analysis: "No continued effectiveness advantage for cemiplimab beyond the maximum treatment duration of 22 months (PFS and OS hazards set equal to those for chemotherapy after this time). As might be expected, this reduces the estimated QALY gain compared with the base case which assumes that relative effects persist for a further three years."	Suggest following revision to the text: "No continued effectiveness advantage for cemiplimab beyond the maximum treatment duration of 22 months (PFS and OS hazards set equal to those for chemotherapy after this time). As might be expected, this reduces the estimated QALY gain compared with the base case which assumes that relative effects persist for a **total of 36 months**."	The current text is not accurate as in the base case of the cost effectiveness analyses a total of 3 years (36 months) of treatment benefit was assumed.	Thank you, we have made the suggested change on page 96.

Page 96 Section 4.3.10.4. Scenario analysis: "Health state utilities from the EXTREME trial (platinum based chemotherapy plus cetuximab for head and neck cancer) 59, as used in TA473. These estimates are lower, with a smaller difference between pre- and post-progression (0.67 and 0.52 respectively) than the estimates from the cemiplimab phase II study used in the company's base case (0.793 and 0.701). " Page 109 Section 4.4.3.2. ERG preferred assumptions Table 40. ERG preferred modelling assumptions: ERG pessimistic scenario, utilities: NICE TA473	Reconsider whether this scenario analysis is appropriate for inclusion in the report.	On page 63 of the ERG report the ERG state: "Our clinical advisors suggested that health-related quality of life and use of supportive care is likely to be quite different for people with head and neck squamous cell carcinoma (HNSCC) or melanomas than for those with CSCC, but that Merkel cell carcinoma and basal cell carcinoma are more comparable." The ERG also note: "For utility and resource use, we compare with information from: • Avelumab for metastatic Merkel cell carcinoma: (TA517) • Vismodegib for metastatic or locally advanced basal cell carcinoma (TA489)" This scenario is not consistent with the ERGs preferred approach.	The CS presents the scenario with TA473 utilities, so it would not be appropriate for us to remove this from section 4.3.10.4. However, we note an error in the cited text from page 96 of the ERG report: the difference between pre and post-progression utilities from TA473 (0.15) is **larger** than that from the cemiplimab phase II study (0.096). We have corrected this mistake. We acknowledge that the utility estimates for HNSCC are not our preferred source. However, pre/post progression utilities are not available for Merkel cell carcinoma, and the estimated decrements for BCC from TA489 are presented separately for locally advanced and metastatic BCC. We therefore use the utility decrement from TA473 in our 'pessimistic' scenario to reflect uncertainty around this parameter. No change made to section 4.4.3.2

Page 107 Section 4.4.3.1 ERG scenario analyses Table 38. ERG additional scenarios: Intervention, additional ERG scenario, cemiplimab costs for weight-based regimen, assuming no vial sharing, and varying mean weight +/- 10% Table 39. ERG scenarios: ERG-corrected company base case, deterministic (at CAA price for cemiplimab): Weight-based cost for cemiplimab Page 109 Section 4.4.3.2. ERG preferred assumptions Table 40. ERG pessimistic scenario, cemiplimab drug costs: Weight-based	Reconsider whether this scenario analysis is appropriate for inclusion in the report.	Although theses analyses are factually accurate we would like to highlight that the anticipated EU marketing authorization for cemiplimab is for a flat dose of 350mg, administered over 30 minutes by intravenous (IV) infusion once every 3 weeks.	Not a factual inaccuracy. No change made. We understand that the anticipated marketing authorisation is for a flat dose, but think it important to also present results with costs for the weight-based regimen, given that the clinical data are for a weight-based dose.

Issue 16 ERG additional scenario analyses

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr><td>Page 141 Appendix 6 ERG analysis results based on the cemiplimab list price:

Confidential information on the cost-effectiveness analyses performed not marked as commercial in confidence.</td><td>Suggest following revision of tables as follows:

Table 1 ERG scenarios: ERG-corrected company base case, deterministic, cemiplimab list price
<table>
<tr><th>Scenario</th><th>Comparator</th><th>Total costs</th><th>Total QALYs</th><th>Pairwise ICERs (cemiplimab vs comparators)</th></tr>
<tr><td>Company base case (ERG corrected)</td><td>Cemiplimab
Chemotherapy
BSC</td><td>[redacted]
[redacted]
[redacted]</td><td>[redacted]
[redacted]
[redacted]</td><td>
[redacted]
[redacted]</td></tr>
<tr><td colspan="5">Patient characteristics</td></tr>
<tr><td>Gender: 75% male</td><td>Cemiplimab
Chemotherapy
BSC</td><td>[redacted]
[redacted]
[redacted]</td><td>[redacted]
[redacted]
[redacted]</td><td>
[redacted]
[redacted]</td></tr>
<tr><td>Gender: 95% male</td><td>Cemiplimab
Chemotherapy
BSC</td><td>[redacted]
[redacted]
[redacted]</td><td>[redacted]
[redacted]
[redacted]</td><td>
[redacted]
[redacted]</td></tr>
<tr><td>Mean age: 60 years</td><td>Cemiplimab
Chemotherapy
BSC</td><td>[redacted]
[redacted]
[redacted]</td><td>[redacted]
[redacted]
[redacted]</td><td>
[redacted]
[redacted]</td></tr>
<tr><td>Mean age: 80 years</td><td>Cemiplimab
Chemotherapy
BSC</td><td>[redacted]
[redacted]
[redacted]</td><td>[redacted]
[redacted]
[redacted]</td><td>
[redacted]
[redacted]</td></tr>
<tr><td colspan="5">Weight-based cost for cemiplimab</td></tr>
<tr><td>Costs for weight-based regimen</td><td>Cemiplimab
Chemotherapy
BSC</td><td>[redacted]
[redacted]
[redacted]</td><td>[redacted]
[redacted]
[redacted]</td><td>
[redacted]
[redacted]</td></tr>
<tr><td>Costs for weight-based regimen with higher mean patient weight (+10%)</td><td>Cemiplimab
Chemotherapy
BSC</td><td>[redacted]
[redacted]
[redacted]</td><td>[redacted]
[redacted]
[redacted]</td><td>
[redacted]
[redacted]</td></tr>
</table></td><td>Contains confidential information on unpublished cost-effectiveness analyses. Additionally, this information could allow calculation of the confidential discount.

ERG response

Apologies for this error. We have added CIC highlighting to the total costs and QALYs in Tables 47 and 49 (ERG report pages 142 to 144).</td></tr>
</table>

	PFS extrapolations				
	Cemiplimab: p1=0; p2=1	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	Cemiplimab: p1=0; p2=-1	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	OS extrapolations				
	Cemiplimab: log-logistic	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	Chemotherapy: p1=0; p2=0	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	Chemotherapy: log-logistic	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	Treatment duration: cemiplimab				
	Treatment cap at 1 year with effects for 2 years	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	No treatment cap with effects for 3 years	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	No treatment cap or limit on duration of effects	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	Adverse events for cemiplimab				
	Annual recurrence of AE cost and QALY loss for duration of treatment effects (3 years)	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]
	As above + equal AE QALY loss and costs for cemiplimab and chemotherapy	Cemiplimab Chemotherapy BSC	[redacted]	[redacted]	[redacted]

Resource use				
Reduced resource use before progression (ERG clinical scenario)	Cemiplimab	[redacted]	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]

Table 2 ERG deterministic modelling scenarios, cemiplimab list price

	Comparator	Total cost	Total QALYs	Pairwise ICERs (cemiplimab vs comparators)
Company base case (ERG corrected)	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
ERG optimistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]
ERG pessimistic	Cemiplimab	[redacted]	[redacted]	
	Chemotherapy	[redacted]	[redacted]	[redacted]
	BSC	[redacted]	[redacted]	[redacted]

References

1. Phillippo DA, Ades AED, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016; http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/Population-adjustment-TSD-FINAL.pdf. Accessed 6 August 2018.
2. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health.* 2011;14(4):539-545.
3. National Institute for Health and Care Excellence. Single Technology Appraisal TA522: Pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable, ERG Report. 2018.

4. Ashby J, O'Hanlon M, Buxton MJ. The time trade-off technique: how do the valuations of breast cancer patients compare to those of other groups? *Qual Life Res.* 1994;3(4):257-265.
5. National Institute for Health and Care Excellence. Single Technology Appraisal TA414: Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. 2016.
6. National Institute for Health and Care Excellence. Single Technology Appraisal TA416: Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer. 2016.
7. Bremner KE, Chong CA, Tomlinson G, Alibhai SM, Krahn MD. A review and meta-analysis of prostate cancer utilities. *Med Decis Making.* 2007;27(3):288-298.
8. Lloyd A, van Hanswijck de Jonge P, Doyle S, Cornes P. Health state utility scores for cancer-related anemia through societal and patient valuations. *Value Health.* 2008;11(7):1178-1185.
9. National Institute for Health and Care Excellence. Single Technology Appraisal TA447: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. 2017.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Tuesday 12 March 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
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- Do not include attachments such as journal articles, letters or leaflets. 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.
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- 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. 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.

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.

About you

Your name	**Gerasimos Konidaris**
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**

Questions for engagement

Issue 1: Definition of the patient population and appropriate comparator(s)	
a) What is the clinical profile of patients in England with advanced CSCC?	The clinical classification of advanced CSCC in England is difficult to define based on published evidence as there is paucity of data on advanced CSCC from public databases and disease registries. Although data is captured in the public domain for non-melanoma skin cancers, it can be challenging to distinguish CSCC from other forms of non-melanoma skin cancers, such as basal cell carcinoma and Merkel cell carcinoma, as these are often grouped together in the coding of patients with a non-melanoma lesion. Based on clinical expert feedback including that from the ERG report, advanced CSCC in England encompasses metastatic CSCC patients and locally advanced CSCC patients who are no longer eligible for curative surgery and curative radiotherapy. These patients are often elderly and frail. According to clinical experts, approximately one third of advanced CSCC patients in England are classified as being immunocompromised, of which most will have had a solid organ transplant with the majority being kidney transplant patients. The remainder of immunocompromised patients will likely have either autoimmune disease (such as rheumatoid arthritis or inflammatory bowel disease), chronic lymphocytic leukaemia (CLL) or viral infection (HIV or Hepatitis B/C). Patients with advanced CSCC in the UK have a particularly poor prognosis with no licenced or effective therapies available to them. There is therefore

	a significant unmet need for a new effective treatment option.
b) Are there any important clinical differences between patients who might be eligible for treatment with cemiplimab/chemotherapy/best supportive care (BSC)?	UK clinical experts during an advisory board conducted by Sanofi advised that currently approximately 25% of advanced CSCC patients will receive platinum based chemotherapy, whilst the remaining 75% are not considered fit enough to tolerate chemotherapy and therefore receive BSC. Clinical experts, during the technical engagement teleconference, highlighted that chemotherapy is characterised by limited clinical efficacy and a high toxicity profile. They suggested that based on the efficacy profile and more manageable safety profile of cemiplimab they anticipate that, once available, cemiplimab would displace the use of chemotherapy in advanced CSCC. They also indicated that a significant proportion of patients currently on BSC would be eligible for treatment with cemiplimab. Eligibility would likely be based on a patient's performance status.
c) What clinical characteristics might mean that treatment with cemiplimab is not appropriate?	Clinical experts during the technical engagement teleconference advised that patients who are severely immunocompromised would not be suitable for treatment with cemiplimab and in particular patients with a solid organ transplant because of the elevated risk of graft rejection. This is in line with the exclusion criteria from the phase II clinical trial of cemiplimab as presented in the Midgen et al 2018[1] publication and the draft summary of product characteristics (SmPC) presented in appendix C of the CS. Other significant exclusion factors to the phase II trial included patients with ongoing or recent evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, prior treatment with an agent that blocks the PD-1/PD-L1 pathway and prior treatment with idelalisib. Based on clinical experts' opinion from the technical engagement teleconference, patients in the real world will not to be considered for

	treatment with cemiplimab if they are considerably frail and have a poor performance status. In the phase II cemiplimab trial, patients were excluded if they had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score ≥ 2.
Issue 2: Generalisability of the clinical evidence for cemiplimab	
a) What is the average age of patients with advanced CSCC?	Clinical experts advising the ERG (ERG report section 4.3.2) noted that the mean age from the cemiplimab trials of 70.4 years, that was used in the economic model, was reasonably reflective of patients seen in routine practice with advanced CSCC not suitable for curative surgery or radiotherapy. However, they also mentioned that the age of patients they see in clinical practice is characterised by a significant variation in line with the range shown in the cemiplimab studies (38 to 96 years). As discussed during the technical engagement teleconference, baseline characteristics of the 106 UK patients captured as part of a retrospective chart review study (further discussed under issue 5 below), conducted by Sanofi, are now available and are reported in Table 10 of the appendix. The mean age of advanced CSCC patients in UK clinical practice was found to be [redacted] years which is consistent with the mean age of 70.4 years from the cemiplimab trials. In addition, Sanofi have become aware of a very recent publication (Sun et al 2019[2]) that may provide relevant evidence for the BSC comparison. Baseline characteristics from the cohort of immunocompetent patients with CSCC that included 20 patients with unresectable lesions, a subset that matches the patients eligible for treatment with cemiplimab, showed a median age of 73 years. Taking the above into account, two scenario analyses have now been added in Table 14 of the appendix. For the first scenario analysis, a mean

	age of 80 years was incorporated in the economic model as requested by the NICE technical team. The second scenario analysis included a mean age of [redacted] in line with the age seen in UK clinical practice based on the retrospective chart review study. Given the available data, Sanofi believe it is appropriate to assume a mean age of ~70 years in the base case analyses.
b) Are the patients that were enrolled in the studies that informed the clinical effectiveness estimates for cemiplimab representative of the UK population with advanced CSCC?	Clinical experts' opinion, as captured in the ERG report (section 4.3.2), suggests that the baseline patient characteristics from the clinical studies of advanced CSCC used in the company's base-case, derived from the cemiplimab clinical trials, are reasonably reflective of the relevant population seen in the NHS but the lack of a UK cohort was noted. Baseline characteristics of the 106 UK patients captured as part of the retrospective chart review (further discussed under issue 5 below), conducted by Sanofi, are now available and are reported in Table 10 of the appendix.
Issue 3: Clinical evidence data source (Integrated analysis or Phase II only)	
Is it appropriate to pool the data from the phase I and phase II studies or are the reasons for excluding the phase I study (the differences in baseline characteristics, exposure to cemiplimab, length of follow-up and extent of prior cancer-related therapy) sufficient to exclude the phase I study?	Sanofi agree with the NICE technical team that pooling the phase I and the phase II cemiplimab trials is appropriate given the small sample sizes and the fact that the phase I trial provides additional follow up data that can increase the power of the clinical data and thus better inform the base-case. However, as the data from the cemiplimab phase II trial matures Sanofi believe that data from this trial alone will become more relevant for decision making. [redacted] Results from this analysis are provided in appendix A.

	This provides an additional [redacted] months of data from that provided in the CS which was based on an October 2017 data cut. This data has been pooled with the phase I data and incorporated into the economic model. A scenario analysis based on the Phase II data only is also provided. As can be seen in Table 14 given the additional follow-up data from the phase II trial the incremental cost-effectiveness ratios (ICERs) when excluding the phase I trial (ICERs equal to £45,269/QALY and £47,038/QALY vs chemotherapy and BSC when only using the phase II trial) are now similar to the ICERs produced when efficacy estimates are derived by the integrated analysis of the two trials (ICERs equal to £45,693/QALY and £47,463/QALY vs chemotherapy and BSC when using pooled data from the phase I and the phase II trials). Additional follow up from the phase II trial supports the conclusions in Sanofi's original submission that cemiplimab, as an end of life medicine, is likely to represent a cost-effective use of NHS resources when compared to the current standard of care.
Issue 4: Quality of the evidence for chemotherapy and best supportive care	
a) Is the assumption that BSC is as clinically effective as chemotherapy conservative? If so is it reasonable?	As described in the CS (section B.3.2.3., page 93), a systematic literature review was conducted in order to identify relevant efficacy and safety evidence for treatments used in advanced CSCC. Given that no evidence was identified for BSC in advanced CSCC, in the base case, clinical data for chemotherapy from the Jarkowski et al study were also used as a proxy for BSC. This approach was further validated with UK clinical experts who considered that although this is a likely conservative assumption it is a reasonable approach given the scarcity of data for advanced CSCC.

	Nevertheless, Sanofi recognised that this approach is characterised by uncertainty and thus provided additional scenario analyses using data from EFGR inhibitor studies as a proxy for BSC in an effort to meaningfully inform the decision making process. This was also deemed to be another reasonable and likely conservative approach on the basis that, as UK experts suggested, these treatments are not expected to be effective in CSCC. These analyses have now been re-run in the economic model following the update of the model with the cemiplimab [redacted] and are provided in Table 14 of the appendix. The resulting ICERs (£40,018/QALY when using data just from EFGR inhibitor studies and £41,068/QALY when using data from the EGFR studies pooled with data form the Jarkowski et al study) are lower than the ICER for the base-case where the Jarkowski data was used as a proxy for BSC (£47,463/QALY). Sanofi have become aware of a very recent publication (Sun et al 2019[2]) that may provide relevant evidence for the BSC comparison. Further detail is provided in appendix G. This new evidence supports the premise that assuming that BSC is as effective as chemotherapy is a conservative assumption and that in reality ICERs for cemiplimab versus BSC are likely to be below those reported above.
b) Are the patients in the Jarkowski et al. 2016 study representative of patients being treated with chemotherapy or BSC in the NHS?	Patients included in the Jarkowski et al study were patients with locally advanced unresectable or metastatic CSCC. This definition is in line with the anticipated cemiplimab licenced population and therefore the population under consideration for this appraisal. Sanofi, however, acknowledge that data based on the Jarkowski et al study are derived from only 18 patients and can be heterogeneous when compared with the population treated in UK clinical practice as well as the population included in the cemiplimab trials. The Jarkowski et al study also only reports data on patients receiving chemotherapy.

	Sanofi believe that data from the ongoing retrospective chart review study will provide an alternative dataset to generate a historical control arm specific to the UK population. The availability of individual patient-level data (IPD) from this study alongside IPD from the cemiplimab trial will allow for more prognostic factors to be adjusted for and thus will enable a more meaningful comparison using indirect treatment comparison (ITC) methodologies.
c) Given the design of Jarkowski et al. 2016 (retrospective chart review) and the size of the sample (N=18) that ultimately informed the base case survival estimates for both chemotherapy and BSC, is this evidence the best available for decision making?	Sanofi consider that currently, given the scarcity of data in advanced CSCC, the Jarkowski et al study provides the best available evidence to inform comparisons versus chemotherapy and subsequently BSC. This view is also in line with the view of the ERG as reflected in the ERG report (section 3.1.7.1., page 40). Sanofi, however, acknowledge the limitations associated with this study and therefore are working on providing clinical data on the current standard of care in advanced CSCC from a retrospective chart review study which will enable comparison with a UK-specific historical control arm once available. Sanofi would like to emphasise that additional scenario analyses were previously provided in order to generate alternative cost-effectiveness estimates with the aim to inform decision making given the uncertainty characterising the base case. In these scenario analyses clinical data from the EGFR studies were used as a proxy for BSC. These analyses have now been re-run in the economic model following the update of the model with the cemiplimab [redacted] and are provided in Table 14 of the appendix. These analyses result in ICERs for cemiplimab versus BSC of £40,018/QALY when using data just from EFGR inhibitor studies and £41,068/QALY when using data from the EGFR studies pooled with data from the Jarkowski et al study. Additionally, long term survival estimates on both cemiplimab and

	chemotherapy derived directly from clinical experts as part of the formal elicitation exercise (described in detail in Section B.3.3.2.2 of the CS) were used in the economic model as a scenario analysis. Sanofi have become aware of a very recent publication (Sun et al 2019[2]) that may provide relevant evidence for the BSC comparison. Further detail is provided in appendix G.
Issue 5: Validity of the company's indirect comparison and value of further comparator data	
a) Given the uncertainty in the STC/MAIC results, is it appropriate to use the naïve comparison to inform the estimate of cost effectiveness of cemiplimab?	As discussed in section B.2.9.4. of the CS, both the STC and the MAIC results are characterised by significant uncertainty. One major limitation has to do with the fact that limited data is available on relevant prognostic factors from the Jarkowski et al study which only allowed for the adjustment of two prognostic factors in the STC. When results from the STC are extrapolated in the economic model, these lead to long term survival estimates which appear to lack clinical validity (given the immaturity of the available data) with OS values of [redacted]% at 60 months. Therefore, in the base case the naïve comparison was used as this produced lower and thus more conservative long term survival estimates given the immature cemiplimab data. It is also important to note that in the CS (section B.3.8.3.) an additional scenario analysis was provided using results from the STC in the economic model. In addition, long term survival estimates on both cemiplimab and chemotherapy derived directly from clinical experts as part of the formal elicitation exercise were used in the economic model as an alternative scenario analysis. Both these approaches generated ICERs for cemiplimab that were more favourable compared to the ones generated in the base case where the naïve comparison is employed.

	Both the simulated treatment comparison (STC) and the matching-adjusted indirect comparisons (MAIC) between cemiplimab and chemotherapy based on the Jarkowski 2016 et al study have been updated using the integrated phase I and II (Groups 1 and 2 only consistently with base-case) data from [redacted]. When the updated STC results are incorporated into the economic model the resulting ICERs (Table 14 of the appendix) of £40,509/QALY vs chemotherapy and £41,916/QALY vs BSC were lower than the updated base-case analyses that were based on naïve comparison.
b) What is the current status of Sanofi's ongoing retrospective chart review study? • How many patients have been recruited? • Are any interim results available – if not, why not? • When is the study likely to be complete?	This study is a retrospective, observational, multi-country, multicenter, cohort study with data abstracted from patient medical records. Further details around the chart review study were provided as a response to clarification question A11. The study is currently underway. Data collection is now completed in most of the participating countries and statistical analyses have been initiated. As can be seen in Table 1 data collection is now completed in the US, UK, Netherlands, France, Germany and Spain. Data collection in Italy is still ongoing. In the UK, a total of 106 case report forms (CRFs) have been completed. **Table 1: Data collection status of the retrospective chart review study** [redacted] Specifically for the UK cohort, as presented in Table 2, it is anticipated that data including PFS and OS will become available in [redacted]. This data will subsequently be incorporated in the ITC followed by integration into the

Status	US	UK	Netherlands	France	Germany	Spain	Italy
Number of sites	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recruited Oncologists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total completed CRFs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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<td>economic model, results of which are expected in [redacted].

Since recruitment in Italy is still ongoing, top line timelines are provided below for Europe and the US. As can be seen, it is anticipated that results from the chart review for all the participating countries will become available in [redacted] with full integration of the data into the ITC and the economic model in [redacted]

Table 2: Detailed timelines on the data availability and incorporation of the chart review study data in the ITC and the economic model
<table>
<tr><th>Action</th><th>Date</th></tr>
<tr><td>Availability of the chart review data from the UK cohort including OS and PFS curves</td><td>[redacted]</td></tr>
<tr><td>Integration of UK chart review data into the ITC</td><td>[redacted]</td></tr>
<tr><td>Integration of UK chart review analysis results into the CEA</td><td>[redacted]</td></tr>
<tr><td>Availability of the chart review data from US and Europe including OS and PFS curves</td><td>[redacted]</td></tr>
<tr><td>Integration of US and European chart review data into the ITC</td><td>[redacted]</td></tr>
<tr><td>Integration of US and European chart review analysis results into the CEA</td><td>[redacted]</td></tr>
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<td>c) Is the population of Sanofi’s ongoing retrospective chart review likely to be representative of patients receiving treatment for advanced CSCC in the NHS?</td>
<td>As can be seen in Table 1 data has been collected from medical records of 106 UK patients with advanced CSCC.

Given that this data was collected across [redacted] different sites in the UK it should be considered to be a good representation of patients treated for advanced CSCC in the NHS. When taking into account the scarcity of data in advanced CSCC it is anticipated that, once available, the results of this analysis will form the best available evidence on the current standard of care to base comparisons on and thus inform the cost-effectiveness</td>
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	analyses. As mentioned during the technical engagement teleconference, aggregate data from the baseline characteristics of the 106 UK patients, captured as part of the retrospective chart review study are now available and are reported in table 10 of the appendix.
d) Will data be available for patients receiving cemiplimab, chemotherapy and best supportive care?	The primary objective of the retrospective chart review study was to evaluate clinical outcomes including overall survival and progression free survival and physician assessed best response for patients diagnosed with advanced CSCC. In line with the eligibility criteria of the retrospective chart review study, medical records from patients with advanced CSCC receiving the current standard of care between 2011 and 2015 were captured retrospectively in Europe (including the UK) and the US. Therefore, no restrictions were applied to the therapies that these patients received as this should represent the current standard of care for patients with advanced CSCC in the clinical practice. As a result, it is anticipated that data collected will include treatments that form the current standard of care in the different participating countries including chemotherapy and best supportive care. Given cemiplimab was neither licenced nor part of the standard of care in any of the participating countries over this period, data captured will not include records of treatment with cemiplimab.
e) How would these additional data reduce the key uncertainties in the current STC/MAIC?	It is anticipated that the ongoing retrospective chart review study will provide an alternative dataset on which to base comparisons versus standard of care and thus inform the cost-effectiveness analyses. The availability of the individual patient-level data (IPD) from this study alongside IPD from the cemiplimab trial will allow for more prognostic

	factors to be adjusted for and thus will enable a more meaningful comparison using indirect treatment comparison (ITC) methodologies. Adjustment of more prognostic factors will reduce the between-study differences and will provide a more robust estimate of the relative treatment effect reducing the uncertainty currently associated with the current STC and MAIC analyses.
Issue 6: Clinical plausibility of the extrapolated overall survival	
a) How clinically plausible are the company's current base-case estimates of overall survival? **Treatment** / **OS at 5 years** / **OS at 10 years** **Cemiplimab** / [redacted] / [redacted] **Chemotherapy/BSC** / [redacted] / [redacted]	Acknowledging the uncertainty associated with the evidence base given the immature data from the cemiplimab trial programme and the limited available evidence on chemotherapy from the Jarkowski et al study, Sanofi adopted an overall conservative approach in the base-case of the cost effectiveness analyses. However, a scenario analysis was also provided in the CS (presented in B.3.8.3, p.161) in which long term survival estimates on both cemiplimab and chemotherapy were derived directly from clinical experts as part of a formal elicitation exercise (described in detail in Section B.3.3.2.2 and appendix M of the CS) and were used in the economic model. When clinical outcomes from the base-case where compared with those from the scenario that included the clinical experts' opinion (section B.3.7.1, page 154) the base case modelled long term survival estimates were found to be more conservative than those incorporating expert opinion and resulted in significantly lower ICERs for cemiplimab. In addition, UK clinical experts consulted at a Sanofi advisory board indicated that survival for advanced CSCC patients treated with chemotherapy in the UK would not exceed 5% at 2 years. The survival estimate from the economic model for chemotherapy at 2 years is [redacted] reinforcing thus that in the base case analysis the assumptions adopted in

	the model could have led to an overestimation of the chemotherapy survival benefit when considering current experience in the UK clinical practice. Taking the above into account but also following discussions with the clinical experts in the technical engagement teleconference who indicated that in their experience advanced CSCC patients do not survive beyond 1 year, Sanofi have conducted a scenario analysis, in line with NICE's request, where survival of patients on chemotherapy is set to 1 year. Results of this exploratory analysis are provided in Table 14 of the appendix and show that the resulting ICER for cemiplimab are £35,029/QALY and £36,093/QALY vs chemotherapy and BSC respectively (compared to £45,693/QALY vs chemotherapy and £47,463/QALY vs BSC in the base case). Again these results highlight that the reported base case ICERs are likely to be conservative and that analyses incorporating clinical opinion may be more suitable for decision making. Additionally, when the latest available cemiplimab data based on the [redacted] is incorporated in the economic model the outcomes generated show consistent results compared to those when using the October 2017 data. This validates the previous extrapolations and the predicted survival for cemiplimab.
b) Is Merkel cell carcinoma a reasonable proxy for advanced CSCC in terms of predicting overall survival (as suggested by the ERG)?	UK clinical experts who participated in the Sanofi advisory board suggested that advanced CSCC is a condition which is distinct to other non-melanoma skin cancers. Experts mentioned that the biology, management and outcomes associated with other cancer types such as basal cell carcinoma, squamous cell carcinoma of the head and neck (SCCHN) and Merkel cell carcinoma (MCC) differ to CSCC. They therefore recommended against using data from these other types of cancer for cost-effectiveness analyses in advanced CSCC.

Issue 7: The maximum duration of treatment (the treatment stopping rule)	
a) In clinical practice, how long would treatment with cemiplimab last? Up to 22 months, 24 months or until progression regardless of when that occurred?	As discussed in the CS (section B.3.3.3.1.), in the base-case, a 22-month stopping rule was applied as this aligned with the design of the phase II cemiplimab trial and consequently with the cemiplimab clinical evidence. A 24-month (2 year) stopping rule was also used as a sensitivity analysis given that this rule is in place for other immunotherapies in the same class as cemiplimab. Sanofi agree with the view of the NICE technical team as expressed in the technical report (issue 7, page 13) that a treatment cap of 24 months is preferred given that this reflects accepted stopping rules in other recent NICE appraisals such as (TA520) Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy and (TA490) Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy. Sanofi would also like to note that the application of a stopping rule in treatment with cemiplimab represents a cost-effective use of cemiplimab in the NHS. When such a stopping rule is employed in the economic model the resulting ICERs are within the accepted willingness-to-pay threshold for an end of life treatment. In line with the discussion during the technical engagement teleconference, and per NICE's request, Sanofi have now provided a series of additional analyses combining the application of different stopping rules (no stopping rule/treat-to-progression, 22-month and 24-month stopping rules) with different assumptions on the persistence of the cemiplimab treatment effect (3 or 5 year benefit) alongside the update of the model with the [redacted] These analyses are reported in Table 14 in the appendix.

b) Would a stopping rule be appropriate or implemented in practice?	In preparation for this appraisal, Sanofi consulted different UK clinical experts in order to better understand the treatment pathway, the unmet need and their experience in treating patients with advanced CSCC. Feedback from UK clinical experts with experience in treating patients with PD-1 inhibitors in other disease areas, where such stopping rules are applied, was that these stopping rules are implementable in clinical practice. They commented that if a recommendation for cemiplimab would include such a stopping rule, the application of this would be straightforward based on the precedent from other PD-1 inhibitors. In addition, in previous immunotherapy appraisals the CDF clinical lead has stated that a 2-year stopping rule is acceptable to both patients and clinicians and is implementable[3,4,5,6,7,8.] It is also worth noting that the licence for these immunotherapies, for which a stopping rule was previously accepted by NICE in the appraisals referenced above, did not include a stopping rule. Similarly, the draft SmPC for cemiplimab does not contain a stopping rule.
c) Regarding chemotherapy how many cycles are patients likely to receive in clinical practice?	Sanofi agree with NICE technical team's preferred assumption to use a 3-cycle treatment for chemotherapy. Following the technical engagement discussion and per NICE's request, the base-case has now been updated in the economic model to include this assumption and results can be found in Table 14 of the appendix.
Issue 8: Persistence of treatment benefits	
a) Is it likely that the treatment effect of cemiplimab will wane over time?	Although there is now compelling evidence that patients' continue to respond to PD-1 treatments after treatment discontinuation[9,10] the duration of the continued benefit is currently uncertain. Indeed previous NICE appraisals have accepted that given the mechanism of action of this class of

	treatments a continued treatment benefit is clinically plausible and have accepted assumption for a persistence of the treatment effect up to 5 years[3,11,4,5,8]. In the CS Sanofi provided a series of scenario analyses where continued benefits are capped at different time points (including 3 and 5 years) but also where a waning effect was applied.
b) The company assumes that the benefit of cemiplimab will last 3 years – is this clinically plausible? If not how long would the benefit be expected to last?	As discussed previously, it is reasonable to expect that cemiplimab, as a PD-1 inhibitor, is associated with a continued treatment benefit. However, the exact duration of this continued benefit beyond the treatment cap proposed for cemiplimab is currently uncertain. In the CS, in the base-case a total 3-year continued benefit was assumed (i.e. an additional continued treatment benefit of 14 months beyond stopping treatment at 22 months as per the applied stopping rule) as this led to more conservative long term survival estimates which were considered appropriate given the current immaturity of the available data. During the technical engagement teleconference, the participating clinical experts did not consider this an unreasonable assumption. However, Sanofi, per NICE's request, have now provided a series of additional analyses combining the application of different stopping rules (no stopping rule, 22-month and 24-month stopping rules) with different assumptions on the persistence of the cemiplimab treatment effect (3 or 5 year benefit) alongside the update of the model with the [redacted]. These analyses are reported in Table 14 of the appendix.
c) Could the next data cut provide information that could reduce uncertainty around persistence of treatment effects of cemiplimab?	Currently there is not sufficient data to fully alleviate the uncertainty around the persistence of the treatment effect of cemiplimab beyond the 22-month treatment cap applied in the phase II trial due to the current duration of follow-up. However additional data from the [redacted] show

	consistent results from the economic model compared to those when using the October 2017 data thus validating the previous extrapolations and the results of the cost-effectiveness analyses. As the data mature, longer term follow up from the cemiplimab phase II trial can provide information on the cemiplimab continued treatment benefit beyond the 22-month treatment cap applied in the trial and help reduce the uncertainty as further discussed in issue 12 below.
Issue 9: Adverse events costs and effect	
a) Is the cost and utility loss due to adverse events likely to be underestimated in the company model or is the current approach acceptable because it has a small impact on the absolute cost and QALY losses?	As discussed during the technical engagement teleconference the assumption adopted in the base-case of the CS was considered appropriate by the clinical experts. To this effect, and following NICE's request, the base-case has now been updated with the [redacted] in the economic model while maintaining this original assumption. Results of this analysis can be found in Tables 12 and 13 of the appendix.

Adverse event	AE rates (% of patients)		AE rates (% of patients)[a]	One off cost (£)
	Cemiplimab	Cemiplimab		
Skin infection	1.1%	NR	0.010	£143.20
Hypercalcaemia	2.1%	NR	0.007	£1,139.92
Failure to thrive	7.7%	NR	0.006	£3,179.70
Fatigue	1.8%	NR	0.006	£3,179.70
Hypokalaemia	1.8%	7.1%	0.007	£1,139.92
Stomatitis or oral mucositis	NR	8.6%	0.013	£998.38
Neutropenia	NR	32.6%	0.007	£325.49
Anaemia	0.9%	14.5%	0.006	£1,273.72
Thrombocytopenia	NR	7.7%	0.009	£325.49
Febrile neutropenia	NR	5.2%	0.008	£2,688.94

b) Should the one-off approach to the disutility of adverse events be accepted given the minimal impact to the absolute cost and QALY loss?	As discussed previously, experts during the technical engagement teleconference considered the one-off approach to the disutility of adverse events a reasonable assumption given the small impact to the absolute cost and QALY loss as well as their experience with dealing with these adverse events in clinical practice.
c) In clinical practice, what are the potential late onset immune related adverse events that can be anticipated?	Clinical experts have stated in clinical practice it is impossible to predict late onset immune related adverse events as they can occur even after treatment has ended. It is worth noting that most immune related adverse events occur earlier on in treatment[12].
Issue 10: Resource use in the pre-progression health state	
Are the estimates of resource use in the pre-progression health state as expected in routine NHS practice?	Sanofi agree with the NICE technical team's preference to use the ERG's assumptions associated with the pre-progression resource use. Following the technical engagement discussion and per NICE's request, the base-case has now been updated in the economic model to include this assumption and results can be found in Tables 12 and 13 of the appendix.
Issue 11: End of Life	
a) What is the current life expectancy of the relevant patient population?	UK clinical experts during the technical engagement teleconference advised that in clinical practice these patients do not survive beyond 1 year in most cases. In line with this discussion and per NICE's request, a scenario analysis has now been conducted where survival of patients on chemotherapy is set at 1 year. Results of this exploratory analysis are provided in Table 14 of the appendix.

	In addition, UK clinical experts consulted at a Sanofi advisory board indicated that survival for advanced CSCC patients treated with chemotherapy in the UK would not exceed 5% at 2 years. There is also potential evidence on survival with BSC in advanced CSCC patients from a recent publication (Sun et al 2019[2]). Median survival of 20 patients with unresectable lesions, a subset that matches the patients eligible for treatment with cemiplimab, was found to be 5 months.
b) How robust are the current estimates of survival benefit?	Although Sanofi acknowledge the uncertainty regarding the current estimates of survival benefit, cemiplimab is very likely to offer more than 3 months survival benefit when compared with the current standard of care in the UK. Indeed modelled survival estimates greatly exceed this showing a survival benefit of [redacted] months compared to current treatment as reported in the CS (section B.2.13.2.). This is further validated by the ERG in the ERG report (section 5, page 113) where, even by using a set of pessimistic assumptions, cemiplimab was found to offer a gain of [redacted] life years ([redacted] months) compared to both chemotherapy and BSC. Additionally, when the latest available cemiplimab data based on the [redacted] is incorporated in the economic model the outcomes generated show consistent results compared to those when using the October 2017 data (survival benefit of [redacted] years; Tables 12 and 13). This further validates the previous extrapolations and the findings regarding survival benefit.
Issue 12: Cancer Drug Fund	
a) Is the technology a good candidate for use in the CDF? Specifically, what additional value can the: • [redacted] data cut of the phase II trial provide in terms of	Sanofi believe that cemiplimab is a potential candidate for use in the CDF given the level of uncertainty with the current evidence and the greater amount of certainty that the proposed data collection is anticipated to

clarifying the uncertainty around overall survival estimates, the treatment stopping rule, the persistence of treatment benefits and the comparability of outcomes across dosing regimens.

- could data collection within the CDF resolve any of the uncertainty?

provide.

A proposed data collection plan was provided in appendix O of the CS.

In order to further support the decision making process, greater clarity on the proposed evidence to be collected, as part of a managed access agreement, is provided below alongside the anticipated issues that this evidence will help address.

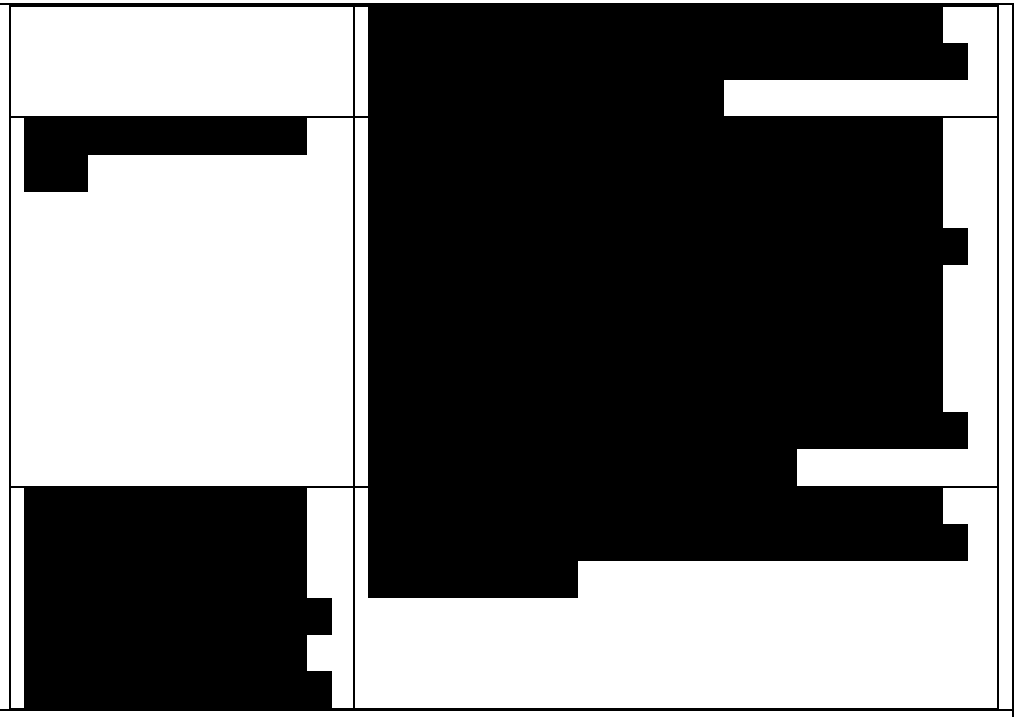
Table 3: Timelines by which the proposed data collection will become available

Proposed data collection	Date when the proposed data is expected to become available
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 4: How the proposed data collection will help address key areas

of uncertainty

Area of uncertainty identified in the technical report	How proposed data collection if recommended for use on the CDF could reduce uncertainty
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

	
b) What can Sanofi's ongoing retrospective chart review provide in terms of clarity around the comparative effectiveness of cemiplimab in the relevant patient population (Issues 3, 5 and 6)?	Data from the retrospective chart review study is anticipated to provide additional evidence on the clinical profile of the patients treated currently in clinical practice alongside data on the survival associated with the current standard of care. Sanofi believe that data from the ongoing retrospective chart review study will provide a more robust dataset to generate a historical control arm specific to the UK population. The availability of the individual patient-level data (IPD) from this study alongside IPD from the cemiplimab trial will allow for more prognostic factors to be adjusted for and thus will enable a more meaningful comparison using indirect treatment comparison (ITC)

methodologies.

Detailed timelines of the availability of the data from the retrospective chart review study both from the UK and the rest of the countries (Europe and the US) are provided below.

Table 5: Detailed timelines on the data availability and incorporation of the chart review study data in the ITC and the economic model

Action	Date
Availability of the chart review data from the UK cohort including OS and PFS curves	[redacted]
Integration of UK chart review data into the ITC	[redacted]
Integration of UK chart review analysis results into the CEA	[redacted]
Availability of the chart review data from US and Europe including OS and PFS curves	[redacted]
Integration of US and European chart review data into the ITC	[redacted]
Integration of US and European chart review analysis results into the CEA	[redacted]

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Appendix A: Updated results from the phase II cemiplimab trial with [redacted]

[redacted]. Efficacy results from this analysis for all groups in the phase II trial (groups 1, 2, and 3) are provided below. This data provides an additional [redacted] months of follow-up over the primary analysis (October 2017 data cut) presented in the company submission (CS).

The data cut-off date for the primary analysis (27 Oct 2017) was defined by the statistical plan for the Group 1 primary endpoint, which required that the last patient enrolled in the group had the potential for approximately 6 months on study. The intent of this 6-month requirement was to ensure that each patient had the opportunity for at least 3 response assessments (performed every 8 weeks) for the primary endpoint. Median duration of follow-up for Group 1 in this updated analysis is [redacted] months. For the patients in Group 2 and Group 3 with sufficient follow-up (opportunity for at least 3 response assessments) to be included in the primary efficacy analysis, median durations of follow up in the updated dataset were [redacted] and [redacted] months, respectively. Median duration of follow-up among all patients in this efficacy analysis is [redacted] months.

At the time of the primary analysis for Group 1 (27 Oct 2017), enrolment was still ongoing for Group 2 (locally advanced CSCC [laCSCC], 3 mg/kg every 2 weeks [Q2W) and Group 3 (mCSCC, 350 mg Q3W). Group 2 completed enrolment on 25 Apr 2018 and Group 3 completed enrolment on 15 Mar 2018. As such, not all patients in these groups had the opportunity for at least 3 response assessments [redacted] Therefore, the updated efficacy results for these groups presented below are for patients who had the opportunity for at least 3 response assessments on study.

Taken together, updated efficacy results for Groups 1, 2, and 3 from the [redacted] further demonstrate the promising efficacy of cemiplimab in advanced

CSCC. In addition, efficacy data are now provided from the Group 3 mCSCC patients treated with the fixed dose regimen of 350 mg Q3W. For a patient population with significant unmet need, the updated data illustrate consistency of overall response rate (ORR) in larger sample sets, and that the responses are sustained with increasing follow-up.

A.1.1. Overall response rate

For the primary endpoint (response rate, per central review), key findings in the phase II study as of the [redacted] data cut-off date are shown in Table 1and Table 2. The numerical differences in objective response rate (ORR) rates between the groups are within the range of expected variability, and the 95% confidence intervals (CI) for ORR overlap broadly. Given that drug concentrations are consistent across all the 3 study groups, response rates between Groups 1, 2, and 3 are due to variability of clinical factors in the patient populations in these groups.

Table 1: Best Overall Tumor Response Rate by Independent central review, for All Patients with Opportunity for ≥3 Response Assessments on phase II study — Full Analysis Set

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	**laCSCC Cemiplimab: 3 mg/kg Q2W (N=64)**	**mCSCC Cemiplimab: 350 mg Q3W (N=44)**	**Total (N=167)**
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]
Objective Response Rate	[redacted]	[redacted]	[redacted]	[redacted]

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=64)	mCSCC Cemiplimab: 350 mg Q3W (N=44)	Total (N=167)
(ORR: CR+PR)				
95% CI for ORR [e]	[redacted]	[redacted]	[redacted]	[redacted]
Data cut-off as of [redacted] [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.				

Duration of response (DOR; per independent central review) is the key secondary endpoint. Table 2 demonstrates that responses to cemiplimab among advanced CSCC patients are durable. Among [redacted] patients with objective responses in Table 2, observed DOR exceeds [redacted] of the patients, and only [redacted] responding patients have experienced progressive disease or death (Table 2). Because of ongoing responses, Table 2 does not account for variable follow-up.

Table 2: Summary of Duration of Response by Independent Central Review for All Patients with Opportunity for ≥3 Response Assessments on Study 1540 - Patients with Confirmed CR or PR — Full Analysis Set

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=29)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=29)	mCSCC Cemiplimab: 350 mg Q3W (N=17)	Total (N=75)
KM Estimation of Duration of Response (CR or PR)				
Number of events, n (%) [a]	[redacted]	[redacted]	[redacted]	[redacted]
Number of censored patients, n (%) [a]	[redacted]	[redacted]	[redacted]	[redacted]
Median months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Observed Duration of Response (CR or PR), n (%)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Min : Max	[redacted]	[redacted]	[redacted]	[redacted]
>=4 months[b]	[redacted]	[redacted]	[redacted]	[redacted]
>=6 months[b]	[redacted]	[redacted]	[redacted]	[redacted]

>=8 months[b]	[redacted]	[redacted]	[redacted]	[redacted]
>=12 months[b]	[redacted]	[redacted]	[redacted]	[redacted]
>= 16 months[b]	[redacted]	[redacted]	[redacted]	[redacted]
>= 20 months[b]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

[a] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.
[b] 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.

A.1.2. Progression-free survival

Progression-free survival (PFS), per independent central review, is summarised for each group in Table 3 and Figure 1. Estimated PFS at 12 months for the total population is [redacted], and the results are highly consistent between the 3 study groups (Figure 1).

Table 3: Kaplan-Meier Estimate of Progression-Free Survival by Independent Central Review for All Patients with Opportunity for ≥3 Response Assessments on Study 1540 — Full Analysis Set

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=64)	mCSCC Cemiplimab: 350 mg Q3W (N=44)	Total (N=167)
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]
[redacted]				

KM = Kaplan- Meier; CI = confidence interval; NE = Not evaluable

Figure 1: Kaplan-Meier Curve for Progression-Free Survival by Independent Central Review for All Patients with Opportunity for ≥3 Response Assessments on Study 1540 – Full Analysis Set

A.1.3. Overall survival

Overall survival (OS) is summarized for each group in Table 4 and

Figure 2. Estimated OS at 12 months for the total population is [redacted]. Kaplan-Meier plots of OS for each group demonstrate that, during the first year on study, [redacted].

Table 4: Kaplan-Meier Estimate of Overall Survival for All Patients with Opportunity for ≥3 Response Assessments on Study 1540 – Full Analysis Set

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=64)	mCSCC Cemiplimab: 350 mg Q3W (N=44)	Total (N=167)

				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]
[redacted]				
KM = Kaplan- Meier; CI = confidence interval; NE = Not evaluable				

Figure 2: Kaplan-Meier Curve for Overall Survival for All Patients with Opportunity for ≥3 Response Assessments on Study 1540 – Full Analysis Set

[redacted]

Appendix B: Update of the simulated treatment comparison (STC) with data from the [redacted]

Both the simulated treatment comparison (STC) and the matching-adjusted indirect comparisons (MAIC) between cemiplimab and chemotherapy based on the Jarkowski 2016 et al study have been updated using the integrated Phase I and II (Groups 1 and 2 only consistently with base-case) data from [redacted]. The methods used were consistent with those included in the original CS. This meant that the core model used for this comparison included disease stage and tumour location, with gender and prior systemic therapy added to the extended model. The core model was found to provide a better overall fit than the extended model for overall survival (OS), progression-free survival (PFS), and response, with results for these analyses presented in Figure 3 to Figure 7.

Figure 3: Unadjusted and population-adjusted Kaplan-Meier curves for overall survival with cemiplimab overlaid with observed curve for chemotherapy with platinum from Jarkowski 2016

Figure 4: Unadjusted and population-adjusted Kaplan-Meier curves for progression-free survival with cemiplimab overlaid with observed curve for chemotherapy with platinum from Jarkowski 2016

Figure 5: Unadjusted and population-adjusted response rates with cemiplimab compared with observed response for chemotherapy with platinum from Jarkowski 2016

Figure 6: Forest plot of hazard ratios of overall survival and progression-free survival for cemiplimab versus chemotherapy with platinum from Jarkowski 2016

Figure 7: Forest plot of odds ratios of response rates for cemiplimab versus chemotherapy with platinum from Jarkowski 2016

Appendix C: Updated PFS and OS inputs included in the cost-effectiveness model based on the [redacted]

In line with the approach followed in the CS, parametric models were fit to both the observed PFS and OS cemiplimab data (the 'naïve comparison'), as well as the 'predicted' cemiplimab PFS and OS for each comparison based on the simulated treatment comparison (STC) using updated efficacy data based on the [redacted].

C.1. Base case: Progression-free and overall survival for cemiplimab based on observed data - naïve comparison (updated based on the integrated Phase I and II [redacted] data)

Figure 8 and

Figure 9 summarise modelled OS and PFS based on alternative parametric distributions fit to the integrated Phase I and II (Groups 1 and 2 only consistently with the base-case in the CS) cemiplimab data from [redacted]. The goodness of fit and plausibility of alternative parametric distributions used to extrapolate OS and PFS

with cemiplimab are summarised in

Table 5 and Table 6. For both OS and PFS, the lognormal was selected for the base case as this was the best fitting distribution in terms of the deviance information criterion (DIC) and also declined over time in a clinically plausible manner. In addition to the base-case analysis, scenario analyses using data only from the Phase II trial are provided in Table 14.

Figure 8: Parametric distributions fit to integrated Phase I and II (groups 1 and 2 only) data, overall survival

Figure 9: Parametric distributions fit to integrated Phase I and II (groups 1 and 2 only) data, progression-free survival

Table 5: Goodness of fit and plausibility of alternative parametric distributions used to estimate overall survival curves with reference treatment (cemiplimab): Base case scenario

Model	Goodness of fit to data		Clinical and epidemiological plausibility of extrapolation	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
Weibull (P1=0)	49.80	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=-1	49.90	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=-0.5	50.07	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=0	50.62	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=0.5	50.74	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=1	51.00	××	[redacted]	[redacted]
P1=1 (Gompertz)	49.53	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=-1	50.43	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=-0.5	50.79	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=0	50.94	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=0.5	51.13	××	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=1	51.35	××	[redacted]	[redacted]
Log-normal	48.50	✓✓	[redacted]	[redacted]
Log-logistic	49.68	✓	[redacted]	[redacted]

Abbreviations: *DIC, Deviance information criterion; OS, overall survival.*

Table 6: Goodness of fit and plausibility of alternative parametric distributions used to estimate progression-free survival curves with reference treatment (cemiplimab): Base case scenario

Model	Goodness of fit to data		Clinical and epidemiological plausibility of extrapolation	
	DIC	Goodness of fit based on DIC	PFS at 60 months	Extrapolation
Weibull (P1=0)	92.88	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=-1	89.95	✓✓	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=-0.5	91.15	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=0	92.61	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=0.5	93.69	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=1	94.47	××	[redacted]	[redacted]
P1=1 (Gompertz)	92.84	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=-1	94.63	××	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=-0.5	94.85	××	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=0	94.41	××	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=0.5	93.83	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=1	92.75	×	[redacted]	[redacted]
Log-normal	89.54	✓✓	[redacted]	[redacted]
Log-logistic	92.78	×	[redacted]	[redacted]

Abbreviations: *DIC, Deviance information criterion; PFS, progression-free survival.*

C.2. Scenario analysis: Progression-free and overall survival for cemiplimab based on population adjusted results from the simulated treatment comparison based on the updated [redacted]

Figure 10 and Figure 11 summarise modelled OS and PFS based on alternative parametric distributions fit to the predicted cemiplimab outcomes that were estimated

through the STC of the Phase I and II (groups 1 and 2 only) data versus Jarkowski 2016. The goodness of fit and plausibility of alternative parametric distributions to extrapolate OS and PFS with cemiplimab are summarised in tables

Table 7 and Table 8. For OS, the Gompertz represented the best fitting distribution in terms of DIC that also declined over time in a clinically plausible manner. For the PFS, the second-order fractional polynomial P1=1, P2=1 represented the best fitting distribution according to DIC.

Figure 10: Parametric distributions fit to population-adjusted Phase I and II (groups 1 and 2 only) data (simulated treatments comparison with Jarkowski 2016), overall survival

Figure 11: Parametric distributions fit to population-adjusted Phase I and II (groups 1 and 2 only) data (simulated treatments comparison with Jarkowski 2016), progression-free survival

Table 7: Goodness of fit and plausibility of alternative parametric distributions used to estimate overall survival curves with reference treatment (cemiplimab): Population-adjusted Phase I and II (groups 1 and 2 only) data using Jarkowski 2016

Model	Goodness of fit to data		Clinical and epidemiological plausibility of extrapolation	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
Weibull (P1=0)	53.01	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=-1	49.95	✓✓	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=-0.5	50.23	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=0	50.34	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=0.5	50.58	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=1	50.98	✓	[redacted]	[redacted]

Model	Goodness of fit to data		Clinical and epidemiological plausibility of extrapolation	
	DIC	Goodness of fit based on DIC	OS at 60 months	Extrapolation
P1=1 (Gompertz)	49.06	✓✓	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=-1	50.84	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=-0.5	50.97	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=0	51.11	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=0.5	51.11	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=1	51.34	×	[redacted]	[redacted]
Log-normal	53.70	×	[redacted]	[redacted]
Log-logistic	56.02	××	[redacted]	[redacted]

Abbreviations: *DIC, Deviance information criterion; OS, overall survival.*

Table 8: Goodness of fit and plausibility of alternative parametric distributions used to estimated PFS curves with reference treatment (cemiplimab): Population-adjusted Phase I and II (groups 1 and 2 only) data using Jarkowski 2016

Model	Goodness of fit to data		Clinical and epidemiological plausibility of extrapolation	
	DIC	Goodness of fit based on DIC	PFS at 60 months	Extrapolation
Weibull (P1=0)	132.25	××	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=-1	133.53	××	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=-0.5	131.91	××	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=0	128.88	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=0.5	124.73	×	[redacted]	[redacted]
Second-order fractional polynomial P1=0, P2=1	120.45	×	[redacted]	[redacted]
P1=1 (Gompertz)	133.96	××	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=-1	130.12	××	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=-0.5	126.15	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=0	120.33	×	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=0.5	114.28	✓	[redacted]	[redacted]
Second-order fractional polynomial P1=1, P2=1	108.88	✓✓	[redacted]	[redacted]
Log-normal	138.00	××	[redacted]	[redacted]
Log-logistic	140.46	××	[redacted]	[redacted]

Abbreviations: *DIC, Deviance information criterion; PFS, progression-free survival.*

Appendix D: Updated health-related quality of life data following the [redacted]

As outlined in the CS, the Longworth mapping algorithm has been used to map data collected from the Phase II cemiplimab study using the EORTC QLQ-30 instrument to the EQ-5D. In line with this approach, as part of the updated base-case analysis, EORTC-QLQ30 values from the [redacted] of the cemiplimab phase II trial were mapped to EQ-5D using the Longworth algorithm.

The utilities generated using the [redacted] from the Phase II study are presented in Table 9. The modelled heath utilities are affected by the updated data in two ways: the addition of new patients, and the addition of extra follow-up for existing patients. In the original data cut (October 2017), maximum follow-up was [redacted] weeks, while in the updated data cut ([redacted]) this increased to [redacted] weeks.

Table 9: Health state utilities estimated using the Phase II data from [redacted]

Health state	Mean	SE
Longworth et al. (2014) algorithm, UK tariff		
Pre-progression	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]

Abbreviations: *SE, standard error.*

Appendix E: Baseline characteristics from the UK cohort of the retrospective chart review study

A retrospective chart review study conducted by Sanofi is currently underway. This study is aimed at gaining a better understanding of the current management and outcomes of advanced CSCC by collecting data from approximately 600 patients in the US and EU, as discussed in Section B.2.11 of the CS. Aggregate data from the baseline characteristics of 106 UK patients, captured as part of the retrospective chart review study are now available and are presented in Table 10.

Table 10: Baseline characteristics of patients identified in the UK chart review

Variable	Levels	N (%)
Age	mean (sd)	[redacted]
Gender	Male	[redacted]
	Female	[redacted]
Prior systemic therapy	No	[redacted]
	Yes	[redacted]
Prior radiation	No	[redacted]
	Yes	[redacted]
AJCC Stage	III	[redacted]
	IV	[redacted]
Tumor	T0	[redacted]
	T1	[redacted]
	T2	[redacted]
	T3	[redacted]
	T4	[redacted]
	TX	[redacted]
ECOG performance status	0	[redacted]
	1	[redacted]
	2	[redacted]
	3	[redacted]
Grade	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	NA	[redacted]
Tumour location	Extremities	[redacted]
	Head and Neck	[redacted]
	Trunk	[redacted]

***Abbreviations**: ECOG, Eastern Cooperative Oncology Group; sd, standard deviation.*

Appendix F: Updated cost effectiveness analyses based on the [redacted]

F.1. Updated modelling assumptions

A summary of all the updated assumptions applied in the updated base-case in the cost-effectiveness model based on the [redacted] data cut is provided in Table 11. The remaining assumptions remained consistent with the ones provided in Table 42 of the CS.

Table 11: Summary of updated modelling assumptions

Assumption	Rationale
Cemiplimab treatment duration: a stopping rule is applied at 24 months – costs of treatment stop at 24 months.	Reflects the NICE technical team's preferred assumption as discussed during the technical engagement teleconference.
Cemiplimab clinical data: overall population from the pooled Phase I and Phase II (EMPOWER-CSCC 1) trials based on the [redacted] data cut.	Best available evidence based on the [redacted]; Phase I data was pooled with phase II EMPOWER-CSCC 1 data as this provides the longest follow-up and increases the sample size. Scenario analyses using data only from the Phase II trial are also provided.
PFS cemiplimab: lognormal distribution	Best fitting distribution on the [redacted] data (according to DIC) that decreases over time and results in clinically plausible long term survival estimates.
OS cemiplimab: lognormal distribution	Best fitting distribution on the [redacted] data (according to DIC) that decreases over time and results in clinically plausible long term survival estimates.
Chemotherapy treatment duration: treatment costs applied up to 3 treatment cycles while the hazard trend continues as per the extrapolated curves.	Updated to reflect the NICE technical team's preferred assumption as discussed during the technical engagement teleconference.
Application of the adverse events remained consistent with the base-case as provided in the CS i.e. one-month duration of effects for all adverse events	Reflects the NICE technical team's preferred assumption as discussed during the technical engagement teleconference.
Source of utilities: EORTC-QLQ30 values from the phase II, EMPOWER I study, based on the [redacted] data cut, were mapped to EQ-5D-3L values using the Longworth *et al*. (2004) mapping algorithm.	In line with the NICE reference case. The phase II, EMPOWER CSCC 1 study ([redacted] data) provides the best available evidence in CSCC. Longworth *et al*. (2004) mapping algorithm provides best predictive ability.
The ERG's preferred approach to the application of pre- and post-progression utilities and the calculation of the age-related utility decrement was incorporated.	In line with the ERG's and the NICE technical team's preferred assumptions.
Updated resource use estimates were used for the pre-progression health state alongside the	Updated to reflect the NICE technical team's preferred assumption as discussed during the

Assumption	Rationale
updated unit costs included by the ERG.	technical engagement teleconference.

F.2. Fixed dose adjustment (used in scenario analysis)

The updated model, based on data from [redacted], incorporates the option to implement an adjustment to the outcomes for the OS and PFS, based on the difference between outcomes in the weighted and fixed dose populations in the Phase II study. Implementing the hazard allows the user to simulate the effect on outcomes of patients receiving the fixed dose versus the weighted dose of cemiplimab while the data for patients in Group 3 (fixed dose) matures. Figure 12 and Figure 13 present OS and PFS for groups 1, 2 and 3 from the Phase II study. The hazard was estimated as the difference in outcomes between Groups 1 and 3. When this option is selected in the model applied a hazard ratio of [redacted] and [redacted] to OS and PFS, respectively.

Figure 12: Overall survival by group in the Phase II study

[redacted]

Figure 13: Progression-free survival by group in the Phase II study

F.3. Hypothetical scenario of mean survival of advanced CSCC patients set at 1 year (scenario analysis)

During the technical engagement teleconference, clinical experts noted that advanced CSCC patients in the UK clinical practice often do not survive beyond one year. In response to this, the NICE technical team requested a hypothetical scenario whereby the mean survival in the comparator arm may be set to 12 months.

The hypothetical chemotherapy arm has been programmed into the model using an exponential distribution with the formula:

$S(t) = \exp(-\lambda t)$

where t is time, and λ is the exponential parameter. The mean of this survival distribution is $1/\lambda$, and so the option has been included in the model parameters page for the user to define the preferred mean survival in this scenario.

When exploring this scenario the cemiplimab arm remains consistent with the base-case approach. Cost-effectiveness results when this scenario is run in the economic model are presented in Table 14.

F.4. Updated base case cost-effectiveness analysis results

Table 12: Discounted base case results versus chemotherapy with the proposed commercial access agreement price for cemiplimab ([redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,693

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 13: Discounted base case results versus best supportive care with the proposed commercial access price for cemiplimab ([redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cemiplimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,463

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

F.5. Scenario analyses from the updated cost-effectiveness model based on the [redacted] data cut

Table 14: Results of key scenario analyses based on the [redacted] data with cemiplimab commercial access agreement price

Base case input	Scenario	ICER versus chemotherapy	ICER versus BSC
Base case results	**N/A**	**45,693**	**47,463**
Comparative efficacy: Naïve	STC[a]	40,509	41,916
24 month stopping rule + 36-month total cemiplimab treatment benefit	24 month stopping rule + 60-month total cemiplimab treatment benefit	39,589	40,996
	22 month stopping rule + 36-month	43,979	45,745

Base case input	Scenario	ICER versus chemotherapy	ICER versus BSC
	total cemiplimab treatment benefit		
	22 month stopping rule + 60-month total cemiplimab treatment benefit	38,214	39,618
	No stopping rule + 36-month total cemiplimab treatment benefit	62,332	64,146
	No stopping rule + 60-month total cemiplimab treatment benefit	60,764	62,215
Source of cemiplimab data: Integrated analysis of phase I and phase II trials (phase II data from Groups 1 and 2)	Phase II + naïve comparison (data from Groups 1 and 2)[a]	45,269	47,038
	Phase II + naïve comparison (data from all cohorts: Groups 1, 2 and 3)[a]	41,961	43,552
	Integrated analysis of phase I and phase II trials (phase II data from all cohorts: Groups 1, 2 and 3)[a]	44,695	46,465
	Integrated analysis of phase I and phase II trials (phase II data from Groups 1 and 2) using the fixed dose adjustment	42,779	44,463
Efficacy of BSC: equal to Chemotherapy based on Jarkowski et al	Pooled EGFR studies	-	40,018
	All studies pooled (EGFR studies plus chemotherapy data from Jarkowski et al)	-	41,068
Survival extrapolations of chemotherapy and BSC: based on the integrated analysis of Jarkowski et al 2016	Mean survival set at 1 year based on clinical experts' feedback during the technical engagement discussion	35,029	36,093
Average patient age at baseline: 70.4 based on the cemiplimab trials	Average patient age at baseline: 80 years (scenario requested by NICE)	55,931	58,323
	Average patient age at baseline: 71.67 years based on the average age from the UK cohort of the retrospective review study	46,506	48,324
[a]using best fitting curves based on DIC			

Appendix G: Evidence from a recent publication on BSC

Sanofi have become aware of a very recent publication (Sun et al 2019[1]) that may provide relevant evidence for the BSC comparison.

The Sun et al 2019 paper reports on a retrospective chart review of 72 patients with cutaneous squamous cell carcinoma of the head and neck who experienced locoregional or distant disease recurrence following surgical resection plus adjuvant radiotherapy (RT). Of the 72 included patients, only 45 had data regarding salvage therapy for the recurrent disease. Of those, 36 out of 45 had unresectable lesions as these were not considered amenable to salvage surgery. A Kaplan-Meier (KM) curve showing overall survival (OS) is available for these 36 unresectable patients (Figure 2 in the Sun et al study). Furthermore, these data are presented separately by immune status (Figure 3 in the Sun et al study). As patients who were immunocompromised would have been excluded from the cemiplimab trials, the data for the 20 immunocompetent patients in Figure 3 is the most suitable for comparison.

This study was published within a timeframe that did not allow full incorporation of the data in the cost-effectiveness model before Sanofi's response to the technical report was due. However overlaid curves that allow a visual inspection of the differences between the survival curves from this study (for the 20 immunocompetent patients), the Jarkowski et al study (data from which was used both for chemotherapy and BSC in the base-case of the CS), the pooled EGFR studies (data from which was used as a proxy for BSC in a scenario analysis in the CS) and the cemiplimab data were plotted in Figure 14.

As can be seen by the curves, the assumptions employed in the base-case, of the cemiplimab cost-effectiveness analysis, regarding the life expectancy associated with BSC (where survival of patients on BSC was assumed to be equal with the survival associated with chemotherapy based on the Jarkowski et al study) are likely to be conservative. Based on these curves it becomes evident that life expectancy for patients with advanced CSCC receiving BSC is considerably lower than the life expectancy observed thus far from the cemiplimab trials.

This new evidence further reinforces that the ICERs produced from the cemiplimab base-case are appropriate for decision making despite the remaining uncertainty.

Indeed the ICERs reported for cemiplimab versus BSC are likely to be overestimates.

Figure 14: Overlaid survival curves for visual inspection against the Sun et al 2019 data

Appendix H: Updated safety data for cemiplimab

As of [redacted], the safety database for cemiplimab in phase I and phase II studies comprised [redacted] patients, including [redacted] patients who received cemiplimab in combination with radiotherapy ± chemotherapy. [redacted]. This monotherapy pool corresponds to safety data which excluded hepatocellular carcinoma (HCC) patients [redacted] from phase I study, in line with the original marketing authorisation application (MAA), but included all patients with other cancer types. As such, this response presents updated safety data for [redacted] patients treated with cemiplimab monotherapy: [redacted].

For the [redacted] patients in phase I and phase II studies who received cemiplimab monotherapy, [redacted] were non-cutaneous squamous cell carcinoma (CSCC) patients and [redacted] were advanced CSCC patients, of whom [redacted] received cemiplimab 350 mg every 3 weeks (Q3W). Hereafter, for ease of reading, the group of monotherapy patients (excluding HCC) will be referred to as “monotherapy patients” or “monotherapy”. All advanced CSCC patients, irrespective of dose, will be referred to as “CSCC patients” and all advanced CSCC patients who received cemiplimab 350 mg Q3W will be referred to as “CSCC 350 mg patients”. Patients with CSCC treated with 350 mg Q3W are a subset of all CSCC patients, who are a subset of all monotherapy patients.

H.1. Exposure to Cemiplimab

As [redacted], the safety data on cemiplimab includes [redacted] patients treated with cemiplimab monotherapy at doses of 1 mg/kg every 2 weeks (Q2W) ([redacted]), 3 mg/kg Q2W ([redacted]), 10 mg/kg Q2W ([redacted]), 200 mg Q2W ([redacted]), and 350 mg Q3W ([redacted]). Of the [redacted] monotherapy patients, [redacted] non CSCC patients were treated with cemiplimab 1 mg/kg Q2W ([redacted]), 3 mg/kg Q2W ([redacted]), 10 mg/kg Q2W ([redacted]), and 200 mg Q2W ([redacted]); and [redacted] CSCC patients were treated with cemiplimab 1 mg/kg Q2W ([redacted]), 3 mg/kg Q2W ([redacted]), and 350 mg Q3W ([redacted]) (Table 15).

The median duration of exposure to cemiplimab in all monotherapy patients was [redacted] weeks (range: [redacted] weeks). The median duration of exposure to cemiplimab for all CSCC patients was [redacted] weeks (range: [redacted] weeks). The median duration of exposure in the CSCC 350 mg patients was [redacted] weeks (range: [redacted] weeks) (Table 16).

A total of [redacted] patients have been exposed to cemiplimab monotherapy for 24 weeks or longer including [redacted] CSCC patients of whom [redacted] were treated with 350 mg Q3W (Table 16). Additionally, [redacted] monotherapy patients have been exposed to cemiplimab for [redacted] weeks or longer, including 75 CSCC patients, [redacted] of whom were treated with cemiplimab 350 mg Q3W.

Table 15: Duration of Exposure to Cemiplimab by Dose Level (Safety Analysis Set)

	CSCC Patients Cemiplimab: 350 mg Q3W		All CSCC Patients		Monotherapy Patients (excluding HCC)	
Dose Level	**n**	**Patient-year**	**n**	**Patient-year**	**n**	**Patient-year**
1 mg/kg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 mg/kg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 mg/kg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
350 mg Q3W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

Table 16: Treatment Exposure for Cemiplimab (Safety Analysis Set)

	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Duration of Exposure (weeks)[a]			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1: Q3	[redacted]	[redacted]	[redacted]
Min : Max	[redacted]	[redacted]	[redacted]
Duration of Exposure, n (%)			
>=0 weeks	[redacted]	[redacted]	[redacted]
>=6 weeks	[redacted]	[redacted]	[redacted]
>=12 weeks	[redacted]	[redacted]	[redacted]
>=24 weeks	[redacted]	[redacted]	[redacted]
>=36 weeks	[redacted]	[redacted]	[redacted]
>=48 weeks	[redacted]	[redacted]	[redacted]
>=60 weeks	[redacted]	[redacted]	[redacted]
>=72 weeks	[redacted]	[redacted]	[redacted]
>=84 weeks	[redacted]	[redacted]	[redacted]

	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
>=96 weeks	[redacted]	[redacted]	[redacted]
[redacted]			

[a] Duration of Exposure (weeks) = Minimum of [last dose date - first dose date + (14 or 21 based on Q2W or Q3W dosing schedule)]/7 AND (data cut-off date or death date - first dose date + 1)/7.

H.2. Adverse events

In all monotherapy patients, [redacted] experienced at least 1 grade ≥3 TEAE. In all CSCC patients, [redacted] patients experienced at least 1 grade ≥3 TEAE while in CSCC 350 mg patients, 21 [redacted] patients experienced at least 1 grade ≥3 TEAE (Table 17). The most common grade ≥3 TEAE (reported in at least [redacted] of all monotherapy patients) were Anaemia, Pneumonia, Cellulitis, Fatigue, Lymphopenia, and Hypertension. The frequency of grade ≥3 TEAE was similar across all groups and consistent with safety data submitted during the original MAA.

In all monotherapy patients, [redacted] patients experienced at least 1 serious TEAE. In all CSCC patients, [redacted] patients experienced at least 1 serious TEAE while in CSCC 350 mg patients, [redacted] patients experienced at least 1 serious TEAE. Common SAEs (that occurred in at [redacted] of all monotherapy patients by preferred term [PT]) were Pneumonitis, Pneumonia, and Cellulitis. This is consistent with safety data submitted with the original MAA.

Table 17: Summary of Most Common (≥2% in Any Group) Grade 3 or Greater Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Total number of Grade 3 or greater TEAEs	[redacted]	[redacted]	[redacted]
Number of Patients with any Grade 3 or greater TEAE , n (%)	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Skin infection	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions			
Fatigue	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]
Vascular disorders			
Hypertension	[redacted]	[redacted]	[redacted]
Nervous system disorders			
Syncope	[redacted]	[redacted]	[redacted]
Renal and urinary disorders			
Haematuria	[redacted]	[redacted]	[redacted]
[redacted]			

TEAE: Treatment-emergent adverse event.
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 monotherapy patients (excluding HCC) group. Within each SOC, PTs are sorted by decreasing frequency in the monotherapy patients (excluding HCC) group.

In all monotherapy patients, [redacted] patients experienced at least 1 serious treatment related TEAE. In all CSCC patients, [redacted] experienced at least 1 treatment related serious TEAE and [redacted] CSCC 350 mg patients experienced at least 1 serious treatment related TEAE. The frequency of serious treatment related TEAEs was similar across all groups.

In all monotherapy patients, [redacted] experienced at least 1 potential irAE, including [redacted] with grade ≥3 events. This is similar to the proportion of all CSCC patients ([redacted] grade ≥3) and CSCC 350 mg patients ([redacted] grade ≥3) who experienced at least 1 potential irAE. The most common potential irAEs (occurring

in at least [redacted] of all monotherapy patients) were Immune-related Skin Adverse Reactions, Immune-related Colitis, and Pruritus. Grade ≥3 potential irAEs that occurred in at least 2 patients in all monotherapy patients were Pneumonitis ([redacted]), Immune-related Hepatitis ([redacted]), and Immune-related Skin Adverse Reaction ([redacted]). The overall frequency and nature of potential irAEs are consistent with safety data in the original MAA.

In all CSCC patients, a TEAE led to permanent treatment discontinuation in [redacted] patients. In CSCC 350 mg patients, a TEAE led to permanent treatment discontinuation in [redacted] patients. No new fatal TEAEs occurred from the data cut-off dates in the original MAA to [redacted].

References

[1] Sun, L., Chin, R.I., Gastman, B., Thorstad, W., Yom, S.S., Reddy, C.A., Nussenbaum, B., Wang, S.J., Knackstedt, T., Vidimos, A.T. and Koyfman, S.A., 2019. Association of Disease Recurrence With Survival Outcomes in Patients With Cutaneous Squamous Cell Carcinoma of the Head and Neck Treated With Multimodality Therapy. *JAMA dermatology*.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Tuesday 12 March 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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. 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.

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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Definition of the patient population and appropriate comparator(s)	
a) What is the clinical profile of patients in England with advanced CSCC?	
b) Are there any important clinical differences between patients who might be eligible for treatment with cemiplimab/chemotherapy/best supportive care (BSC)?	
c) What clinical characteristics might mean that treatment with cemiplimab is not appropriate?	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. There is lack of robust data for patients with advanced cutaneous SCC (cSCC) in terms of available systemic treatment options and their efficacy. The phase I and II data of Cemiplimab shows promise in terms of response and impact on survival, although immature. The results seen are the best available thus far. Thus Cemiplimab provides data in this area of unmet need. The survival estimates from the 2 clinical studies show a similar pattern (tail of the curve) seen with immunotherapy in other tumour sites. However, we do not think it is reasonable to compare the survival seen in patients with cSCC with that seen in patients with Merkel cell carcinoma (MCC). This is because MCCs are aggressive tumours which are biologically different from cSCC.

Issue 2: Generalisability of the clinical evidence for cemiplimab	
a) What is the average age of patients with advanced CSCC?	
b) Are the patients that were enrolled in the studies that informed the clinical effectiveness estimates for cemiplimab representative of the UK population with advanced CSCC?	
Issue 3: Clinical evidence data source (Integrated analysis or Phase II only)	
Is it appropriate to pool the data from the phase I and phase II studies or are the reasons for excluding the phase I study (the differences in baseline characteristics, exposure to cemiplimab, length of follow-up and extent of prior cancer-related therapy) sufficient to exclude the phase I study?	
Issue 4: Quality of the evidence for chemotherapy and best supportive care	
a) Is the assumption that BSC is as clinically effective as chemotherapy conservative? If so is it reasonable?	
b) Are the patients in the Jarkowski et al. 2016 study representative of patients being treated with chemotherapy or BSC in the NHS?	
c) Given the design of Jarkowski et al. 2016 (retrospective chart review) and the size of the sample (N=18) that ultimately informed the base case survival estimates for both chemotherapy and BSC, is this evidence the best available for decision making?	
Issue 5: Validity of the company's indirect comparison and value of further comparator data	
a) Given the uncertainty in the STC/MAIC results, is it appropriate to use the naïve comparison to inform the estimate of cost effectiveness of cemiplimab?	

b) What is the current status of Sanofi's ongoing retrospective chart review study? • How many patients have been recruited? • Are any interim results available – if not, why not? • When is the study likely to be complete?	
c) Is the population of Sanofi's ongoing retrospective chart review likely to be representative of patients receiving treatment for advanced CSCC in the NHS?	
d) Will data be available for patients receiving cemiplimab, chemotherapy and best supportive care?	
e) How would these additional data reduce the key uncertainties in the current STC/MAIC?	
Issue 6: Clinical plausibility of the extrapolated overall survival	
a) How clinically plausible are the company's current base-case estimates of overall survival?	
b) Is Merkel cell carcinoma a reasonable proxy for advanced CSCC in terms of predicting overall survival (as suggested by the ERG)?	
Issue 7: The maximum duration of treatment (the treatment stopping rule)	
a) In clinical practice, how long would treatment with cemiplimab last? Up to 22 months, 24 months or until progression regardless of when that occurred?	

Treatment	OS at 5 years	OS at 10 years
Cemiplimab	[redacted]	[redacted]
Chemotherapy/BSC	[redacted]	[redacted]

b) Would a stopping rule be appropriate or implemented in practice?	
c) Regarding chemotherapy how many cycles are patients likely to receive in clinical practice?	
Issue 8: Persistence of treatment benefits	
a) Is it likely that the treatment effect of cemiplimab will wane over time?	
b) The company assumes that the benefit of cemiplimab will last 3 years – is this clinically plausible? If not how long would the benefit be expected to last?	
c) Could the next data cut provide information that could reduce uncertainty around persistence of treatment effects of cemiplimab?	
Issue 9: Adverse events costs and effect	
a) Is the cost and utility loss due to adverse events likely to be underestimated in the company model or is the current approach acceptable because it has a small impact on the absolute cost and QALY losses?	

Adverse event	AE rates (% of patients)		AE rates (% of patients)[a]	One off cost (£)
	Cemiplimab	Cemiplimab		
Skin infection	1.1%	NR	0.010	£143.20
Hypercalcaemia	2.1%	NR	0.007	£1,139.92
Failure to thrive	7.7%	NR	0.006	£3,179.70
Fatigue	1.8%	NR	0.006	£3,179.70
Hypokalaemia	1.8%	7.1%	0.007	£1,139.92
Stomatitis or oral mucositis	NR	8.6%	0.013	£998.38
Neutropenia	NR	32.6%	0.007	£325.49

Anaemia	0.9%	14.5%	0.006	£1,273.72
Thrombocytopenia	NR	7.7%	0.009	£325.49
Febrile neutropenia	NR	5.2%	0.008	£2,688.94

b) Should the one-off approach to the disutility of adverse events be accepted given the minimal impact to the absolute cost and QALY loss?	
c) In clinical practice, what are the potential late onset immune related adverse events that can be anticipated?	
Issue 10: Resource use in the pre-progression health state	
Are the estimates of resource use in the pre-progression health state as expected in routine NHS practice?	
Issue 11: End of Life	
a) What is the current life expectancy of the relevant patient population?	
b) How robust are the current estimates of survival benefit?	
Issue 12: Cancer Drug Fund	
a) Is the technology a good candidate for use in the CDF? Specifically, what additional value can the: • [redacted] data cut of the phase II trial provide in terms of clarifying the uncertainty around overall survival estimates, the treatment stopping rule, the persistence of treatment benefits and the comparability of	In the context of lack of standard systemic therapy options, ICERs calculations will need to be compared with best supportive care and will not be considered cost-effective. If Cemiplimab is not approved for inclusion on the CDF, we will never be able to progress in our quest for better systemic options to treat advanced cSCC.

outcomes across dosing regimens. • could data collection within the CDF resolve any of the uncertainty?	Moreover, the inclusion of Cemiplimab on the CDF will enable us to get real world prospective data on the advanced cSCC which would be more robust than the retrospective data collection. Hence, in order for the patients not to be deprived of Cemiplimab, we would support the inclusion of Cemiplimab on the CDF, even if it is for a limited time period of 2-3 years.
b) What can Sanofi's ongoing retrospective chart review provide in terms of clarity around the comparative effectiveness of cemiplimab in the relevant patient population (Issues 3, 5 and 6)?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Tuesday 12 March 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 [redacted], all information submitted under [redacted]. 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.

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.

About you

Your name	**Charlotte Proby**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Physicians, NCRI Skin Cancer Clinical Studies Group**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Definition of the patient population and appropriate comparator(s)	
a) What is the clinical profile of patients in England with advanced CSCC?	The majority are elderly (and often frail) or immunosuppressed. There will be some (rare) younger immunocompetent patients (see 2a).
b) Are there any important clinical differences between patients who might be eligible for treatment with cemiplimab/chemotherapy/best supportive care (BSC)?	Yes, PD1 inhibitors are much better tolerated than chemotherapy in this elderly population. I would expect there to be patients for whom cemiplimab was appropriate, but chemotherapy is not.
c) What clinical characteristics might mean that treatment with cemiplimab is not appropriate?	Not appropriate for solid organ transplant recipients, nor for some patients with a history of significant autoimmune disease. Also, best supportive care may be the only appropriate treatment if a very frail elderly patient i.e. would not consider Cemiplimab if ECOG 3 or 4.
Issue 2: Generalisability of the clinical evidence for cemiplimab	
a) What is the average age of patients with advanced CSCC?	Majority 70-90 years. Could be significantly younger if a genetic predisposing risk such as xeroderma pigmentosa or recessive dystrophic epidermolysis bullosa.
b) Are the patients that were enrolled in the studies that informed the clinical effectiveness estimates for cemiplimab representative of the UK population with advanced CSCC?	Yes, I believe so

Issue 3: Clinical evidence data source (Integrated analysis or Phase II only)	
Is it appropriate to pool the data from the phase I and phase II studies or are the reasons for excluding the phase I study (the differences in baseline characteristics, exposure to cemiplimab, length of follow-up and extent of prior cancer-related therapy) sufficient to exclude the phase I study?	Appropriate to pool the data. The differences in baseline characteristics are not sufficient to exclude phase I data.
Issue 4: Quality of the evidence for chemotherapy and best supportive care	
a) Is the assumption that BSC is as clinically effective as chemotherapy conservative? If so is it reasonable?	In the majority of cases chemotherapy does not prolong life more than a few months and does not improve quality of life. On this basis it is reasonable to consider chemotherapy as equivalent to BSC, although in real life chemotherapy is possibly worse than death for the patient. If Cemiplimab were licensed for treatment of CSCC in the UK, I think oncologists would cease to use chemotherapy.
b) Are the patients in the Jarkowski et al. 2016 study representative of patients being treated with chemotherapy or BSC in the NHS?	Yes and no. I think the Jarkowski study has many flaws including the very small number of patients suggesting they were highly selected and the retrospective nature, both introducing potentially high levels of bias. I am concerned that the modelling based on this study has given a totally unrealistic life expectancy after treatment with chemotherapy (mean [redacted] years). This is not real-life experience in the UK where these patients die within 12 months with or without chemotherapy.
c) Given the design of Jarkowski et al. 2016 (retrospective chart review) and the size of the sample (N=18) that ultimately informed the base case	There is almost no evidence on outcomes for advanced CSCC treated with chemotherapy. There is more evidence with EGFR inhibitors, but

survival estimates for both chemotherapy and BSC, is this evidence the best available for decision making?	again low patient numbers and uncontrolled trials. Pooled data for EGFR inhibitors suggests ORR 7-28% and median PFS only 3.8-4.7 months. There are no robust data, i.e. no prospective or randomised controlled trials for advanced CSCC. As described in 4b, I have serious reservations about using the Jarkowski study for informing the base case survival estimates for either chemotherapy or BSC. I think the retrospective chart review on UK patients that should be available by early [redacted] will be better for decision making, else perform an audit of UK oncologists who treat this disease and ask them for the survival outcomes on the last 3 patients with advanced CSCC treated.
Issue 5: Validity of the company's indirect comparison and value of further comparator data	
a) Given the uncertainty in the STC/MAIC results, is it appropriate to use the naïve comparison to inform the estimate of cost effectiveness of cemiplimab?	Yes, I think you have to use the naïve comparison to estimate cost effectiveness, despite the immaturity of the data and hope additional data over the next period will help to reduce the uncertainties.
b) What is the current status of Sanofi's ongoing retrospective chart review study? • How many patients have been recruited? • Are any interim results available – if not, why not? • When is the study likely to be complete?	We have been told by Sanofi that enrolled patients from the UK (n=106) will be analysed first and that information on survival outcomes should be available from early [redacted]. Unclear when the study will complete as it includes patients from other European countries and the US as well as the UK. Aiming for 600 patients in total, I believe.

c) Is the population of Sanofi's ongoing retrospective chart review likely to be representative of patients receiving treatment for advanced CSCC in the NHS?	Yes, I believe so. Baseline characteristics are already available so generalisability can be assessed now.
d) Will data be available for patients receiving cemiplimab, chemotherapy and best supportive care?	There won't be data on Cemiplimab from the retrospective chart review. There should be data on chemotherapy and BSC and this should help inform the base case survival estimates and reduce some of the uncertainty for incremental LYG. The interim data cut for the Phase II Cemiplimab study (from June 2018) should be available soon and should include more mature data for Cemiplimab as well as early data for patients on fixed dose regimens. This will reduce some of the uncertainty, although these fixed dose patients are few in number.
e) How would these additional data reduce the key uncertainties in the current STC/MAIC?	Better data to inform the base case survival estimates.
Issue 6: Clinical plausibility of the extrapolated overall survival	
a) How clinically plausible are the company's current base-case estimates of overall survival?	The Cemiplimab estimates are plausible although the data are too immature to confirm currently. Learning from other PD-1 inhibitors, we might expect to see a long tail in the response arm. Whether this will be at 40% or 20% is not known and clearly makes a big difference to overall survival. The Chemotherapy/BSC estimates appear much too optimistic. There will be very few (if any) patients alive at 5 or 10 years. There may be the occasional patient who survives, but this will be due to individual idiosyncracy, probably related to an inherent immune

Treatment	OS at 5 years	OS at 10 years
Cemiplimab	[redacted]	[redacted]
Chemotherapy/BSC	[redacted]	[redacted]

	response against the cancer and, for these few cases, OS at 10 years may be similar to OS at 5 years. Basically, chemotherapy does not work in this disease and without effective treatment, patients will die.
b) Is Merkel cell carcinoma a reasonable proxy for advanced CSCC in terms of predicting overall survival (as suggested by the ERG)?	I'm not sure that it is. Merkel cell carcinoma (MCC) is inherently a highly aggressive malignancy, but it is driven by a virus (polyomavirus) and is both very sensitive to radiotherapy and to immune checkpoint inhibitors such as PD1 inhibitors. The virally-driven biology of MCC makes it very different from CSCC and might make it more sensitive to anti-PD1 blockade. However, the highly aggressive behaviour of MCC might predicate to a worse overall survival. Hard to predict which of these scenarios is true so yes, it could be a reasonably proxy for advanced CSCC, but equally it may behave entirely differently.
Issue 7: The maximum duration of treatment (the treatment stopping rule)	
a) In clinical practice, how long would treatment with cemiplimab last? Up to 22 months, 24 months or until progression regardless of when that occurred?	If it works well as the early data suggests it will ([redacted] ORR), then patients will wish to continue treatment until progression. Anecdotal data from patients on dual immunotherapy who had to stop treatment because of immune-related toxicities, suggests that there may be prolonged benefits even after stopping treatment so a treatment stopping rule seems reasonable.

b) Would a stopping rule be appropriate or implemented in practice?	I believe a stopping rule is appropriate, however I also think it will be difficult to implement in practice. This treatment is very well tolerated and patients will want to continue with it.
c) Regarding chemotherapy how many cycles are patients likely to receive in clinical practice?	3 cycles is probably a reasonable estimate as this treatment is poorly tolerated in this elderly population.
Issue 8: Persistence of treatment benefits	
a) Is it likely that the treatment effect of cemiplimab will wane over time?	Interim data from the Phase II study may help inform this. Data from other immune checkpoint inhibitors suggests that a proportion of patients will show a very durable response, possibly for years.
b) The company assumes that the benefit of cemiplimab will last 3 years – is this clinically plausible? If not how long would the benefit be expected to last?	Yes, 3 years is plausible, if treatment given for 22-24 months. I think 3 years is a reasonable estimate for a median response. However, this estimate may be too conservative. It could be longer especially if treatment given until disease progression.
c) Could the next data cut provide information that could reduce uncertainty around persistence of treatment effects of cemiplimab?	Yes, if data continues to be collected from Phase I study patients as these patients discontinued treatment after 11 months (48 weeks).
Issue 9: Adverse events costs and effect	
a) Is the cost and utility loss due to adverse events likely to be underestimated in the company model or is the current approach acceptable because it has a small impact on the absolute cost and QALY losses?	No, I don't think it is underestimated. These PD1 inhibitors are usually well tolerated and the late immune-mediated AEs are well recognised

Adverse event	AE rates (% of patients)		AE rates (% of patients)[a]	One off cost (£)
	Cemiplimab	Cemiplimab		
Skin infection	1.1%	NR	0.010	£143.20
Hypercalcaemia	2.1%	NR	0.007	£1,139.92
Failure to thrive	7.7%	NR	0.006	£3,179.70
Fatigue	1.8%	NR	0.006	£3,179.70
Hypokalaemia	1.8%	7.1%	0.007	£1,139.92
Stomatitis or oral mucositis	NR	8.6%	0.013	£998.38
Neutropenia	NR	32.6%	0.007	£325.49
Anaemia	0.9%	14.5%	0.006	£1,273.72
Thrombocytopenia	NR	7.7%	0.009	£325.49
Febrile neutropenia	NR	5.2%	0.008	£2,688.94

and relatively easy to treat inexpensively (e.g. thyroxine for hypo-thyroiditis or dexamethasone for hypo-adrenalism).

b) Should the one-off approach to the disutility of adverse events be accepted given the minimal impact to the absolute cost and QALY loss?	Yes
c) In clinical practice, what are the potential late onset immune related adverse events that can be anticipated?	Extrapolating to other immune checkpoint inhibitors (Pembrolizumab) they include skin rash (itching), endocrine dysfunction (lots of different symptoms), lung toxicity (cough, shortness of breath), GI toxicity (diarrhoea, stomach pain, GI bleeding), cardiac toxicity (chest pain, shortness of breath), muscle aches and joint pain, hepatitis, anaemia, easy bruising. Despite this long list, individually these are not so frequent and are well recognised by oncologists plus there are relatively

	simple treatments (e.g. glucocorticosteroids) that can be given to ameliorate.
Issue 10: Resource use in the pre-progression health state	
Are the estimates of resource use in the pre-progression health state as expected in routine NHS practice?	I agree that the ERG estimates for pre-progression resource use are more likely to reflect NHS practice.
Issue 11: End of Life	
a) What is the current life expectancy of the relevant patient population?	Several months to 12 months maximum except in exceptional cases.
b) How robust are the current estimates of survival benefit?	Not robust. I think they underestimate the comparative benefit afforded by Cemiplimab because they overestimate the benefit from BSC or chemotherapy.
Issue 12: Cancer Drug Fund	
a) Is the technology a good candidate for use in the CDF? Specifically, what additional value can the: • [redacted] data cut of the phase II trial provide in terms of clarifying the uncertainty around overall survival estimates, the treatment stopping rule, the persistence of treatment benefits and the comparability of outcomes across dosing regimens. • could data collection within the CDF resolve any of the uncertainty?	Yes, I believe it is a good candidate for use in the CDF. The [redacted] data cut will be too immature to give comparability of outcomes across dosing regimens. Data collected within the CDF should resolve this uncertainty. Phase I trial data (if collected and available) will give better clarification of persistence of treatment benefits after stopping treatment (as stopped after 48 weeks). Phase II trial data will give some clarification around survival outcomes and PFS, but it will still be

	immature and median OS may not be reached if a tail (plateau in durable response) is demonstrated. This will create difficulty for ERG comparisons, but will reinforce the effectiveness of this treatment and show persistence of treatment benefits. Data collection within the CDF should help resolve uncertainty around overall survival estimates, persistence of treatment benefits and comparability of outcomes across different dosing regimens. Uncertainty around the treatment stopping rule will not be resolved if the drug is licensed for use until progression.
b) What can Sanofi's ongoing retrospective chart review provide in terms of clarity around the comparative effectiveness of cemiplimab in the relevant patient population (Issues 3, 5 and 6)?	This will provide essential data on which to estimate baseline survival for the comparative effectiveness of Cemiplimab (issues 5 & 6). Data on baseline characteristics and generalisability will (I predict) support the appropriateness of combining data from Phase I and Phase II studies (issue 3). There won't be data available on Cemiplimab from the chart review, but more mature data should become available from the Phase I and II studies. The most helpful data will be survival data for patients who received chemotherapy or BSC (issue 5). The population examined in the retrospective chart review should be representative of patients receiving treatment for advanced CSCC in the NHS (issue 5). These data will also inform the companies extrapolated overall survival for chemotherapy/BSC, which I believe are unrealistic (issue 6).

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma

ERG critique of company updated analyses in response to the NICE Technical Engagement Report

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed 25th March 2019

This report contains confidential information. Highlighting indicates information that is [redacted] or [redacted].

1 Introduction

In response to the consultation on the NICE Technical Engagement (TE) Report, the company has updated their clinical effectiveness and cost effectiveness analyses and provided some additional information. Specifically, the company has provided:

- An updated economic analysis model based on data from a more recent data cut in the phase II study.
- Responses to each of 12 issues identified by NICE during the TE consultation process, tabulated in the NICE TE Response Form.
- Eight Appendices (A to H) that provide additional information and results of the company's updated analyses.

This report presents the ERG's critique of the company's responses to the NICE TE consultation. The report has two main sections:

- Section 2: ERG's comments on the company's tabulated responses to each of the 12 specific issues raised by NICE in the TE Response Form.
- Section 3: ERG's comments on the additional data and analyses provided by the company in their Appendices A to H.

The updated analyses provided by the company are based on the latest available data cut in their phase II study ([redacted]). The previous (interim) data cut used to support the company's analyses in their original submission was in October 2017. The main implications of the new data provided by the company are: (1) the available sample size for the cemiplimab studies has increased; (2) the duration of follow-up of the cemiplimab studies has increased; and (3) a previously-excluded fixed-dose group of mCSCC patients in the phase II study has been included in the company's updated analyses.

1.1 Sample size

The sample sizes for each of the groups included in the company's original analyses (October 2017 data cut) and updated analyses ([redacted] data cut) are shown in Table 1. The company has not explicitly stated how many patients have been enrolled into the phase II study, with the exception of Group 1 (N=59) which had completed enrolment by October 2017, as reported in the original company submission (CS).

Table 1 Sample sizes for the company's original submission and updated analyses

Study/group	Used in original submission (based on phase II study 27 Oct 2017 data cut)	Used in post-engagement submission (based on phase II study [redacted] data cut)
Phase I study	26	26
Phase II (all enrolled patients)	137 [b]	Not reported
• Group 1 (mCSCC)	59 [b]	59
• Group 2 (laCSCC)	55 [b]	Not reported
• Group 3 (mCSCC fixed dose)	23 [b]	Not reported
Phase II (full analysis set [FAS])[a]	82 [b]	167 [C]
• Group 1 (mCSCC)	59 [b]	59 [C]
• Group 2 (laCSCC)	23 [b]	64 [C]
• Group 3 (mCSCC fixed dose)	0 [b]	44 [C]
Base case integrated analysis (phase I patients plus phase II groups 1 and 2 FAS patients)	N=108	N=149

[a] In the original CS, Group 2 patients were only included in the FAS if they had completed 9 months of follow-up. None of the patients in Group 3 were included in the FAS in the original CS on the grounds that the data were very immature (see section 1.3 below). According to company Appendix A, Group 2 and 3 patients were only included in the FAS if they had had the opportunity for at least 3 response assessments.

[b] According to Figure 7 in the original CS.

[c] According to Tables 1, 3, and 4 in company Appendix A.

We note that the company have not been consistent in the groups that they have included in their analyses. Their updated analysis of data from the cemiplimab studies, reported in company Appendix A, is based on the phase II study alone (including the fixed-dose group) (see section 3.1 below). However, their updated indirect treatment comparison (ITC) analysis, reported in company Appendix B, is based on the integrated analysis as defined in their original submission, which includes the phase I study but excludes the fixed-dose group of the phase II study (see section 3.2 below). As these analyses differ in their sample sizes and the inclusion/exclusion of the fixed-dose group the ERG would have preferred to see both analyses presented in company Appendices A and B.

The updated progression free survival (PFS) and overall survival (OS) curves reported in company Appendix C and the base case economic results reported in company Appendix F are based on the integrated analysis. However, the company also report cost-effectiveness results for scenarios using Phase II data only (groups 1 and 2; and groups 1, 2 and 3) and Phase I and II data (groups 1, 2 and 3). See section 3.6 below.

1.2 Duration of follow up

The durations of follow-up for each of the study groups included in the company's original and updated analyses are shown in Table 2. Company Appendix A states that the updated data analysis including patients who received the weight-based dose of cemiplimab (Groups 1 and 2) and those who received the fixed-dose (Group 3) provides an additional [redacted] months of follow-up compared to the analysis that was presented in the CS (October 2017 data cut).

Table 2 Median duration of follow-up (months) compared between the company's original submission and updated analyses

Study/group	Original submission (based on phase II study 27 Oct 2017 data cut)	Post-engagement submission (based on phase II study [redacted] data cut)
Phase I study	[redacted] [a]	Not reported
Phase II study, overall (FAS)	[redacted] [b]	[redacted] [e]
• Group 1 (mCSCC)	[redacted] [c]	[redacted]
• Group 2 (laCSCC)	[redacted] [c]	[redacted] [e]
• Group 3 (mCSCC fixed dose)	[redacted] [d]	[redacted] [e]
Integrated analysis (FAS)	[redacted] [f]	Not reported

[a] From original CS Appendix Table 15.

[b] From original CS section B.3.3.

[c] From clarification question response A4.

[d] From clarification question response A10 – this group not analysed due to immature follow-up.

[e] From company Appendix A.

[f] From clinical study report.

1.3 Inclusion of the fixed-dose mCSCC group

A key difference between the company's original submission and their updated analysis is that Group 3 in the phase II study, in which patients received a fixed cemiplimab dose (350 mg q3w), was excluded from the company's original CS analyses but has been included in the updated analyses. The company's rationale for not initially including this group was that the data were too immature, as enrolment was incomplete (original CS Table 3) and median follow-up at the October 2017 data cut-off was only [redacted]) months (clarification question response A10). Enrolment to Group 3 was completed in March 2018, meaning that those patients who received the fixed-dose regimen and had sufficient follow-up (≥3 months) at the [redacted] data cut-off were available for the latest analysis (N=44). The fixed-dose group reflects the dose regimen in the company's anticipated marketing authorisation. Whilst this group has now been included in the company's analyses, it represents only 26% of the patients in the phase II study FAS, with the majority (74%) having received the weight-based dose.

2 ERG critique of the company's response to issues identified in the NICE Technical Engagement Report

2.1 Issue 1: Definition of the patient population and appropriate comparator(s)

Considerations	ERG comments
1a. What is the clinical profile of patients in England with advanced CSCC?	The company has not provided any new information. Their responses are consistent with their original submission and concur with the opinions of clinical experts in the NICE TE teleconference.
1b. Are there any important clinical differences between patients who might be eligible for treatment with cemiplimab/ chemotherapy/ best supportive care (BSC)?	
1c.What clinical characteristics might mean that treatment with cemiplimab is not appropriate?	

2.2 Issue 2: Generalisability of the clinical evidence for cemiplimab

Considerations	ERG comments
2a. What is the average age of patients with advanced CSCC?	The company have provided two new age estimates: (1) The mean age of UK patients in their retrospective chart review study was [redacted] years (N=106), but median age is not reported. (2) The median age of a small subgroup of advanced CSCC patients (N=20) in a newly-published retrospective study (Sun et al. 2019) was 73 years – but this was in a USA population. The company have conducted two new scenario analyses: (1) assuming a mean age of 80 years (per NICE request) and (2) assuming a mean age of [redacted] years (see section 3.6 below).
2b. Are the patients that were enrolled in the studies that informed the clinical effectiveness estimates for cemiplimab representative of the UK population with advanced CSCC?	The company have cited existing information in the ERG report. No new information is presented here regarding the representativeness of patients enrolled in studies providing estimates of the clinical effectiveness of cemiplimab.

2.3 Issue 3: Clinical evidence data source (Integrated analysis or Phase II only)

Considerations	ERG comments
Is it appropriate to pool the data from the phase I and phase II studies or are the reasons for excluding the phase I study (the differences in baseline characteristics, exposure to cemiplimab, length of follow-up and extent of prior cancer-related therapy) sufficient to exclude the phase I study?	The company's response suggests that the main reason for pooling the phase I and phase II studies was to improve the small sample size and the short duration of follow up. The company state that as the data from the phase II study mature this study alone will become "more relevant" for decision making, but they do not provide a justification for this or discuss the implications of excluding the phase I study. The company have updated the integrated analysis outcomes from the cemiplimab studies with an additional [redacted] months of phase II study data from a data cut of [redacted] (base case). They have also provided a scenario analysis based on the updated phase II study data only. The company incorporated these updated data into the economic model and the cost-effectiveness results in Table 14 in company Appendix F (see section 3.6 below).

2.4 Issue 4: Quality of the evidence for chemotherapy and best supportive care

Considerations	ERG comments
4a. Is the assumption that BSC is as clinically effective as chemotherapy conservative? If so is it reasonable?	The company refer to existing information in their CS in support of the assumption that BSC is as clinically effective as chemotherapy (CS section B.3.2.3). In addition: (1) The company have updated their scenario analyses that used EGFR inhibitor studies as a proxy for BSC, with the latest phase II study data ([redacted] data cut). The resulting ICERs reported in Table 14 of Appendix F indicate that the ICER is higher when data for chemotherapy rather than EGFR inhibitors are used as a proxy for BSC (see section 3.6 below). (2) The company cite data from a small BSC subgroup (N=20) in a newly-published retrospective study (Sun et al. 2019) which gives a shorter median overall survival (OS) estimate for the BSC group when compared to the chemotherapy group in the comparator (Jarkowski et al. 2016) study.
4b. Are the patients in the Jarkowski et al. 2016 study representative of patients being treated with chemotherapy or BSC in the NHS?	The company acknowledge that the Jarkowski et al. 2016 study data may not be representative for patients treated in the NHS (small sample size, non-UK population, limited population characteristics data). They argue that data from their ongoing retrospective chart review study will provide a more relevant UK-specific population with a larger sample size, although these data are not yet available.
4c. Given the design of Jarkowski et al. 2016 (retrospective chart review) and the size of the sample (N=18) that ultimately informed the base case survival estimates for both chemotherapy and BSC, is this evidence the best available for decision making?	The company refer to existing information in their CS and the ERG report to support their argument that the Jarkowski et al. 2016 study currently provides the best evidence to inform comparisons versus chemotherapy and, by proxy, versus BSC. In addition: (1) The company cite the newly-published retrospective study of patients with advanced CSCC in the USA (Sun et al. 2019) which provides OS data for a small subgroup of BSC patients (N=20). This study does not inform any of the company's cost-effectiveness analyses carried out to date. However, the company have provided a visual comparison of OS curves observed in: (i) the Sun et al. 2019 study BSC subgroup, (ii) the Jarkowski et al. 2016 chemotherapy study, (iii) pooled EGFR inhibitor scenario analysis (BSC proxy), and (iv) the cemiplimab phase I and phase II studies (Figure 14 in Appendix G) (see section 3.7 below). (2) The company state that data from their ongoing retrospective chart review study will provide more relevant data on the UK current standard of care (updated analyses are anticipated in [redacted]).

2.5 Issue 5: Validity of the company's indirect comparison and value of further comparator data

Considerations	ERG comments
5a. Given the uncertainty in the STC/MAIC results, is it appropriate to use the naïve comparison to inform the estimate of cost effectiveness of cemiplimab?	The company acknowledge the uncertainty in the matched adjusted indirect comparison (MAIC) and simulated treatment comparison (STC), and note information in the original CS suggesting that the STC extrapolation led to implausible OS estimates. The company have updated their analyses using phase II study data from the latest data cut ([redacted]) which demonstrates that the naïve comparison produces a higher ICER than the STC (Table 14 in Appendix F). The company justify their selection of the naïve analysis as it provides a more conservative ICER, but they do not provide a statistical rationale for why a naïve comparison would be appropriate. Both the company and ERG agreed prior to this updated analysis that all results from the ITC analyses are highly uncertain due to the inability of all the analysis approaches to account for key confounding factors, and the updated analysis does not reduce this uncertainty.
5b. What is the current status of Sanofi's ongoing retrospective chart review study? - How many patients have been recruited? - Are any interim results available – if not, why not? - When is the study likely to be complete?	The company confirm that all (N=106) UK patients have now been included in the retrospective chart review study, from [redacted] sites involving [redacted] oncologists. Data are currently unavailable as statistical analyses are ongoing. Data are anticipated to be available in [redacted] and the results of updated economic analyses including these data are expected to be available in [redacted]. The retrospective chart review study covers a population that was sampled during 2011-2015. The ERG is unclear why the data are not yet available, more than three years after sampling ended.
5c. Is the population of Sanofi's ongoing retrospective chart review likely to be representative of patients receiving treatment for advanced CSCC in the NHS?	The retrospective chart review study includes UK patients and the eligibility criteria (reported by the company in clarification question response A11) are consistent with the company's decision problem. Therefore, the patients included in the study should be representative of patients receiving treatment for advanced CSCC in the NHS. However, the company has not reported the process for selection of the sites so it is unclear where these were located, how the sites/oncologists were recruited (e.g. whether any incentives were involved), and whether there were any relevant sites/oncologists that were not selected.

	It is also unclear what the length of follow-up was for patients included in the retrospective chart review (not reported in the study eligibility criteria in clarification question response A11). The company have provided aggregate baseline characteristics data for the 106 patients included in the retrospective chart review study in Table 10 in Appendix E. We have provided a table below to enable comparison of these characteristics against those of the Jarkowski et al. 2016 chemotherapy study and those of the cemiplimab integrated analysis (Table 6 below). Some differences are evident between the baseline characteristics of patients included in the retrospective chart review and those included in the cemiplimab integrated analysis (section 3.5 below).
5d. Will data be available for patients receiving cemiplimab, chemotherapy and best supportive care?	The company confirm that the retrospective chart review study will provide data for patients who received standard of care during 2011-2015 (i.e. current standard of care), which would include BSC and chemotherapy but not cemiplimab.
5e. How would these additional data reduce the key uncertainties in the current STC/MAIC?	The company state that the retrospective chart review would reduce uncertainty in the ITC since the individual patient data (IPD) would enable more prognostic factors to be adjusted for. The aggregate baseline characteristics data provided by the company which we have reproduced in Table 6 below suggest that at least 5 prognostic factors would be available in both the retrospective chart review and the cemiplimab integrated (or phase II study) analyses that could be considered for statistical adjustment (section 3.5 below). Additionally, the retrospective chart review study would further reduce statistical uncertainty by increasing the sample size in the ITC analyses, and the population would be more reflective of a real-world UK population.

2.6 Issue 6: Clinical plausibility of the extrapolated overall survival

Considerations	ERG comments
6a. How clinically plausible are the company's current base-case estimates of overall survival?	The company argue that their estimates of OS for patients on chemotherapy are conservative, citing analyses conducted in their original CS. Additionally, the company acknowledge clinical expert opinion in the NICE TE teleconference that patients with advanced CSCC do not survive beyond 1 year. They conducted a scenario analysis (per NICE request) in which mean OS was set to 1 year, based on data from the latest ([redacted]) data cut. Results of this

	analysis, presented in Table 14 in Appendix F, gave lower ICERs than the base case (see section 3.6 below).
6b. Is Merkel cell carcinoma a reasonable proxy for advanced CSCC in terms of predicting overall survival (as suggested by the ERG)?	The company argue that basal cell carcinoma, squamous cell carcinoma of the head and neck (SCCHN) and Merkel cell carcinoma (MCC) are different to CSCC and therefore are not appropriate sources of proxy data for advanced CSCC in cost-effectiveness analyses. We note that these are very different cancers. For instance, SCCHN (depending on how it is defined) can include non-skin cancers such as those of the larynx. We agree that SCCHN may not be an appropriate source of proxy data for advanced CSCC. However, clinical experts advising the ERG suggested that patients with advanced Merkel cell carcinoma would be more comparable to advanced CSCC patients in terms of their poor prognosis and lack of treatment options (ERG Report section 4.2).

2.7 Issue 7: The maximum duration of treatment (the treatment stopping rule)

Considerations	ERG comments
7a. In clinical practice, how long would treatment with cemiplimab last? Up to 22 months, 24 months or until progression regardless of when that occurred?	In the anticipated marketing authorisation, cemiplimab would be used until disease progression or unacceptable toxicity; although clinical expert opinion in the NICE TE teleconference was that a 2-year treatment duration would be more reflective of clinical practice. The company acknowledge that some of the uncertainty in the cost-effectiveness results relates to the duration of cemiplimab treatment (and persistence of treatment effects) and they have conducted scenario analyses around these assumptions (Table 14 in company Appendix F). For their base case, they appropriately applied a stopping rule of 24 months, reflecting NICE's preferred assumption.
7b. Would a stopping rule be appropriate or implemented in practice?	The ERG agrees with the company.
7c. Regarding chemotherapy how many cycles are patients likely to receive in clinical practice?	The company have appropriately applied treatment costs of chemotherapy up to 3 cycles. This reflects clinical practice and NICE's preferred assumption.

2.8 Issue 8: Persistence of treatment benefits

Considerations	ERG comments
8a. Is it likely that the treatment effect of cemiplimab will wane over time?	The company cite previous appraisals for PD-1 inhibitor treatments where the assumption of persistence of treatment effect up to 5 years have been accepted. For their base case analyses, the company have assumed persistence of the treatment benefit for 36 months. This conservative scenario aligns with the clinical advice in the NICE TE teleconference. The company have also conducted scenario analyses where the treatment effect persists up to 60 months.
8b. The company assumes that the benefit of cemiplimab will last 3 years – is this clinically plausible? If not how long would the benefit be expected to last?	The company's assumption reflects clinical opinion in the NICE TE teleconference.
8c. Could the next data cut provide information that could reduce uncertainty around persistence of treatment effects of cemiplimab?	The company acknowledge the uncertainty around the persistence of the treatment effect of cemiplimab beyond the 22-month treatment cap in the phase II study. We agree with the company that longer term follow up data from the phase II study would reduce the uncertainty around the persistence of the treatment effect.

2.9 Issue 9: Adverse events costs and effect

Considerations	ERG comments
9a. Is the cost and utility loss due to adverse events likely to be underestimated in the company model or is the current approach acceptable because it has a small impact on the absolute cost and QALY losses?	The company do not directly address the question of whether the cost or utility loss due to adverse events (AEs) are underestimated in their model, or refer to the table of AE rates, disutilities and costs in the Technical Engagement response form. They note that their revised economic results in Tables 12 and 13 of Appendix F are updated with [redacted] data, while maintaining their "original assumption" (presumably referring to the assumption of a one-off cost and utility loss for adverse events). We note that despite reporting updated AE rates for

	cemiplimab based on the [redacted] safety dataset (company Appendix H.2 and section 3.8 below), the company have not revised the AE estimates in their model. The ERG still considers that the impact of AEs is likely to be underestimated in the company's revised cost-effectiveness estimates, as costs and effects of late onset AEs are omitted. However, we do not expect that this would significant impact on the ICER estimates, as absolute AE rates, and the associated costs and utility losses are small.
9b. Should the one-off approach to the disutility of adverse events be accepted given the minimal impact to the absolute cost and QALY loss?	The company notes that experts in the technical engagement teleconference considered that the one-off approach to modelling AE costs and utility loss is reasonable given their small impact on cost and QALY results. The company continues to apply the one-off approach in their revised base case analysis, and do not report results with the ERG scenario assuming annual recurrence of AE costs and disutilities. As noted above, the ERG does not think that this is likely to have a significant impact on ICER estimates.
9c. In clinical practice, what are the potential late onset immune related adverse events that can be anticipated?	The company states that most immune related adverse events occur earlier in treatment (Haanen et al 2017), but that it is impossible to predict late onset immune related AEs, as they can occur after treatment has ended.

2.10 Issue 10: Resource use in the pre-progression health state

Considerations	ERG comments
Are the estimates of resource use in the pre-progression health state as expected in routine NHS practice?	The company have appropriately applied resource use estimates for the pre-progression health state along with updated unit costs in their updated base case analyses for the [redacted] data cut. Their updated base case model reflects NICE's preferred assumptions and is consistent with clinical practice.

2.11 Issue 11: End of Life

Considerations	ERG comments
11a. What is the current life expectancy of the relevant patient population?	The company note that according to UK expert opinion in the NICE TE teleconference, most patients with advanced CSCC do not currently survive beyond 1 year. The company also report that UK clinical experts at an advisory board estimated 2-year survival at no more than 5%; and a median survival of 5.0 months in a retrospective study in the USA (Sun et al. 2019) for the subset of immunocompetent advanced CSCC patients with disease recurrence who were not eligible for surgery (n=20). These estimates contrast with results from the revised company base case model, which predicts a mean survival of [redacted] years (undiscounted) with chemotherapy based on the Jarkowski et al data, or [redacted] years using the EGFR inhibitory proxy for best supportive care. The ERG considers that all the available survival estimates are subject to high uncertainty.
11b. How robust are the current estimates of survival benefit?	The company acknowledges that estimates of OS are uncertain but that the ERG's "pessimistic" scenario analysis (ERG report section 5) estimated OS gain with cemiplimab at [redacted] months. The ERG report noted that median OS was not reached in the cemiplimab studies after a median of [redacted] months of follow-up and that the estimated 16-month OS rate was [redacted]. We concluded that cemiplimab likely offers a life-extending treatment for patients with a short life expectancy. The company's revised analysis with data from the latest cut ([redacted]) does not alter this conclusion. This produces a mean (undiscounted) gain of [redacted] life years for chemotherapy (Jarkowski data); or [redacted] years with the EGFR proxy data for best supportive care. However, once again we emphasise that estimates of OS gain should be treated with caution due to the lack of robust comparative clinical data.

2.12 Issue 12: Cancer Drugs Fund

Considerations	ERG comments
12a. Is the technology a good candidate for use in the CDF? Specifically, what additional value can the: - [redacted] data cut of the phase II trial provide in terms of clarifying the uncertainty around overall survival estimates, the treatment stopping rule, the persistence of treatment benefits and the comparability of outcomes across dosing regimens. - could data collection within the CDF resolve any of the uncertainty?	The company believe cemiplimab is a good candidate for the CDF. They have provided details of the data that they propose to collect in order to resolve the uncertainty in the clinical effectiveness and cost effectiveness of cemiplimab (Tables 3 and 4 within the NICE TE Response Form). However, the company have not directly answered NICE's question regarding how much of the uncertainty would be resolved by the [redacted] data cut of the phase II study in relation to uncertainty around OS estimates, the stopping rule, and persistence of benefits. We note that full data from the fixed-dose group of the phase II study, which reflects the dose regimen in the company's anticipated marketing authorisation, is not expected to be available until a data cut in [redacted] (with analysis expected in [redacted]). We further note that the fixed-dose group only includes patients with metastatic CSCC patients and the company has not commented on whether any 350mg q3w fixed-dose data would be collected for patients with locally advanced CSCC.
12b. What can Sanofi's ongoing retrospective chart review provide in terms of clarity around the comparative effectiveness of cemiplimab in the relevant patient population (Issues 3, 5 and 6)?	The company state that IPD from the ongoing retrospective chart review study will allow for more prognostic factors to be adjusted for in the ITC. The company do not indicate which factors they expect could be adjusted for. As noted above (section 2.5, Issue 5e), we believe that, based on the aggregate data available at present, at least five prognostic factors might be available for both the cemiplimab and retrospective chart review studies for consideration. Additionally, some statistical uncertainty may be reduced by the larger sample size of the retrospective chart review comparator data set compared to the existing Jarkoswki et al. 2016 study. The retrospective chart review study, being on a UK population, would also be more clinically relevant than the Jarkowski et al. 2016 study.

3 Additional ERG comments on the company's updated analyses

The company have provided eight appendices which report: updated cemiplimab clinical effectiveness data from the [redacted] phase II study data cut (Appendix A); updated STC analyses based on these data (Appendix B); updated PFS and OS curves based on these data (Appendix C); updated HRQoL data and utility mapping (Appendix D); baseline population characteristics of the company's ongoing retrospective chart review study (Appendix E); updated cost-effectiveness analyses (Appendix F); OS data for BSC patients in the new study by Sun et al. 2016 (Appendix G); and updated safety data (Appendix H). Our comments on each of these appendices are provided below in sections 3.1 to 3.8.

3.1 ERG comments on company Appendix A (updated cemiplimab study data)

The company have presented updated results for response rates, duration of response (DOR), progression-free survival (PFS) and OS based on the [redacted] data cut for all study groups in the phase II study. These updated analyses differ from those reported in the original CS, since they include the fixed-dose group of the phase II study (Group 3) but exclude the phase I study. The rationale for including the fixed-dose group is discussed above in section 1.3, whilst the rationale for excluding the phase I study is considered above in section 2.3.

The updated analyses provide an increase in the sample size (see Table 1 above) and an increase in the duration of follow-up (see Table 2 above). The company state that the new data provide an additional [redacted] months of follow-up compared to the analyses in their original CS.

The updated analyses indicate a slight increase in the objective response rate (ORR), which was the primary outcome of the phase II study, but with very wide 95% confidence intervals (Table 3). We note (data not shown) that the proportion of complete responses has increased in mCSCC Group 1 (from 6.8% to [redacted]%) and in laCSCC Group 2 (from [redacted]% to [redacted]%) but in mCSCC Group 3 (fixed dose) there were no complete responses after a median of [redacted] months of follow-up. Based on Kaplan-Meier (KM) estimates in the updated analysis, median DOR had only been reached in Group 1 ([redacted] months). These response data do not inform the company's economic analyses.

Median PFS was not reached in the original analysis but in the updated analysis ranged from [redacted] months in mCSCC patients receiving fixed-dose cemiplimab (Group 3) to [redacted]

months in mCSCC patients who received the weight-based cemiplimab dose (Group 1) (Table 4)

Table 3 ORR, % (95% CI) for original and updated analyses

Analysis	mCSCC, Group 1	laCSCC, Group 2	mCSCC, fixed dose, Group 3
Original analysis	47.5 (34.3 to 60.9) n=59	[redacted] n=23	No data
Updated analysis	[redacted] n=59	[redacted] n=64	[redacted] n=44

Table 4 Median PFS, months (95% CI) for original and updated analyses

Analysis	mCSCC, Group 1	laCSCC, Group 2	mCSCC, fixed dose, Group 3
Original analysis	Not reached (n=59)	Not reached (n=23)	No data
Updated analysis	[redacted] n=59	[redacted] n=64	[redacted] n=44
NE: not evaluable			

Median OS has not yet been reached for any of the study groups in the company's updated analysis.

3.2 ERG comments on company Appendix B (updated STC analyses)

The company have updated their original STC, MAIC and naïve indirect comparisons with data from the [redacted] data cut of the phase II study. However, these are based on the integrated analysis population as defined in their original submission, which includes the phase I and phase II studies but excludes the fixed-dose group of the phase II study (total sample size N=149). This is inconsistent with the updated cemiplimab analysis reported in company Appendix A (total sample size N=167). The company have not explained why they have selected the smaller of these two analysis populations for matching in the ITC analyses.

Compared to the company's original submission, the updated data provide a larger sample size (see Table 1) and longer duration of follow-up (see Table 2). However, the statistical methods followed by the company are the same as those employed in their original ITC analyses, which both the company and ERG agreed have major weaknesses, particularly the limited ability to match the cemiplimab IPD to the Jarkowski et al. 2016 comparator study, which itself is unlikely to represent a UK real-world population. Only two prognostic

factors could be adjusted for in the ITC core model, and the Jarkowski et al. 2016 study chemotherapy comparator group had a sample size of only 18 patients, as well as being retrospective so potentially at risk of selection bias. Thus, the high uncertainty around the results is not resolved by these updated analyses.

The company has provided KM curves for OS and PFS and forest plots for OS, PFS and ORR (Figures 3 to 7 in Appendix B) for each of the STC, MAIC and naïve comparisons. These are for the integrated analysis, i.e. using data pooled from both the phase I and phase II studies but excluding the fixed-dose group of the phase II study, so are directly comparable with the company's original analyses. Due to the high uncertainty around these outcomes we have not reproduced them here.

3.3 ERG comments on company Appendix C (updated PFS and OS curves)

The company has fitted fractional polynomial (FP) survival curves to the [redacted] PFS and OS data for cemiplimab. For the base case, they use curves fitted to the integrated dataset: comprising phase I and phase II (groups 1 and 2 only) data, without adjustment for differences between the cemiplimab and chemotherapy study samples (naïve comparison). Figures 8 and 9 in company Appendix C illustrate the wide range of OS and PFS extrapolations fitted to these data, and Tables 5 and 6 summarise key statistics related to the goodness of fit (DIC), 5-year survival rates and hazard trends.

The company have chosen to use a ***lognormal*** distribution for both OS ([redacted] at 5 years) and PFS ([redacted] at 5 years) in their base case, arguing that these functions have the best fit to the observed data (lowest DIC scores) and decline over time in a clinically plausible manner. We agree that these are functions are plausible but note that other functions with declining (but non-zero) hazards have similar DIC statistics, including the ***Weibull*** and the ***second-order FP with P1=0 and P2=-1***: which produce 5-year survival estimates in the range of [redacted] and [redacted] for OS and [redacted] to [redacted] for PFS. The company does not present any scenario analyses for alternative OS/PFS extrapolations in the cemiplimab arm.

For comparison, the survival extrapolations in the revised base case are slightly more favourable than those in the original company base case: which used a lognormal for OS ([redacted] at 5 year) and Weibull for PFS ([redacted] at 5 years). We show the company's Kaplan-Meier (KM) curves and selected fitted curves from the original and updated data cut for OS and PFS (naïve comparison) in Figure 1 and Figure 2 below.

Figure 1 Progression-free survival extrapolations for cemiplimab: original and updated company base case (KM and selected extrapolations)

Figure 2 Overall survival extrapolations for cemiplimab: original and updated company base case (KM and selected extrapolations)

The company presents scenarios for OS and PFS functions fitted to alternative data sets:

- Phase I and phase II study data (groups 1 and 2 only), STC adjusted comparison;
- Phase I and phase II study data (groups 1, 2 and 3), naïve comparison;
- Phase II study data only (groups 1 and 2 only), naïve comparison;
- Phase II study data only (groups 1, 2 and 3), naïve comparison.

Information about the fitted OS and PFS curves with STC adjustment is provided in the company appendix section C.2. As noted above (section 3.2), we consider the STC to be too unreliable for consideration. The choice between the alternative data sets for use in the model is less clear-cut, although on balance we consider the integrated data set including all three groups from the phase II study to be most appropriate, as this includes a proportion of patients receiving fixed dose of cemiplimab, as in the anticipated market authourisation.

PFS and OS extrapolations for the modelled comparator arms (based on Jarkowski chemotherapy data and the alternative EGFR inhibitor proxy for best supportive care) remain unchanged from the company's original submission. These data are highly uncertain, but the company does not present any scenario analysis in their technical engagement response to reflect the impact of this uncertainty on their ICER estimates.

3.4 ERG comments on company Appendix D (updated HRQoL data)

The company incorporated additional EORTC QLC-30 data from the most recent Phase II data cut, which they mapped to EQ-5D-3L (UK tariff) using the Longworth algorithm – as in the original submission. They did not provide any information about the additional data, other than noting that it increased the number of patients and average length of follow up. See Table 5 below for the original and updated mapped health state utility estimates.

Table 5 Utility estimates from phase II EORTC data (Longworth algorithm)

Health state	October 2017 data cut		[redacted] data cut	
	Mean	SE	Mean	SE
Pre-progression	0.793	0.019	[redacted]	[redacted]
Post-progression	0.701	0.062	[redacted]	[redacted]
Progression disutility	0.092		[redacted]	

As in the company's original analysis, the mapped pre-progression utility exceeds general population values (Health Survey for England means, adjusted for the age and gender mix of the modelled cohort). In their revised model, the company follows the ERG approach of

setting pre-progression utilities equal to general population means (from Health Survey for England data, adjusted for age and gender mix). Post-progression utility is then estimated by subtracting the decrement from the mapped estimates: 0.092 in the CS analysis and [redacted] in the updated analysis. This has the effect of reducing ICER estimates compared with the original company analyses, as a higher utility is applied in the post-progression state.

3.5 ERG comments on company Appendix E (retrospective chart review study baseline data)

The company's retrospective chart review study is currently ongoing and is anticipated to provide comparator data for an update of the company's indirect comparison in [redacted]. Company Appendix E is therefore not relevant to any of the analyses that the company has conducted to date. It does, however, provide an insight into the types and extent of information that may be available later in the NICE appraisal process.

The company intends to use IPD from their retrospective chart review study to inform an updated ITC in [redacted]. Table 6 below compares the aggregate population characteristics of the UK cohort of the retrospective chart review study against those data available from the current cemiplimab integrated analysis and the current chemotherapy comparator study (Jarkowski et al. 2016). Assuming that the aggregate data reflect the minimum set of prognostic factors that would be available in the IPD, then at least five prognostic factors would be available in both the retrospective chart review and the cemiplimab integrated (or phase II study) analyses for statistical adjustment (ECOG PS, prior cancer-related therapy, prior cancer-related radiotherapy, tumour location [e.g. % head and neck], and tumour site [laCSCC, mCSCC]). Additionally, the retrospective chart review study would further reduce statistical uncertainty by virtue of its larger sample size and would reduce clinical uncertainty due to its more realistic UK setting. Note that the company's analysis in [redacted] may not utilise the integrated analysis, as their preference is to exclude the phase I study.

Some differences are evident between the baseline characteristics of patients included in the retrospective chart review and those included in the cemiplimab integrated analysis, regarding patients who had prior systemic therapy ([redacted] versus [redacted]), patients who had prior radiation therapy ([redacted] versus [redacted]) and the distribution of ECOG PS (PS ≥2: [redacted] versus [redacted]).

Table 6 Baseline characteristics compared for the cemiplimab integrated analysis, retrospective chart review and Jarkowski study

Baseline characteristic	Integrated analysis: N=108 (from CS Table 5 unless stated otherwise)	Retrospective chart review UK patients: N=106 (from Table 10 in Appendix E)	Jarkowski study [a]all patients N=25, [b]platinum chemotherapy patients N=18 (from CS Appendix Table 9)
Age, median, years	[redacted]	Not reported	66.4 [a]
Age, mean, years	Not reported	[redacted]	Not reported
Sex, male %	[redacted]	[redacted]	72 [a]
Weight, mean kg	[redacted]	Not reported	Not reported
ECOG PS	[redacted]	[redacted]	Not reported
Prior cancer related systemic therapy %	[redacted]	[redacted]	Platinum chemotherapy: 100 [b]
Prior cancer related radiotherapy%	[redacted]	[redacted]	Not reported
Prior cancer related surgery %	[redacted]	Not reported	Not reported
Number of regimens at baseline	[redacted]	Not reported	Not reported
Tumour stage (T0 – TX) %	Not reported	T0: [redacted] T3: [redacted] T1: [redacted] T4: [redacted] T2: [redacted] TX: [redacted]	Not reported
Tumour grade (1 – 4) %	Not reported	1: [redacted] 4: [redacted] 2: [redacted] NA: [redacted] 3: [redacted]	Not reported
Tumour location (head/neck/trunk) %	Head & neck: [redacted] Trunk: Not reported (source: integrated analysis CSR 4.3.2)	Head & neck: [redacted] Trunk: [redacted]	Head & neck: 44 [a] Trunk: 28 [a]
Tumour site	laCSCC: 30.6 mCSCC: 69.4	Not reported (but data available?)	laCSCC: [redacted] [b] mCSCC: [redacted] [b]

As noted above (section 2.5, Issue 5c), the company have not explained how the sites/oncologists included in the study were selected.

3.6 ERG comments on company Appendix F (updated cost-effectiveness analyses)

3.6.1 Appendix F.1. Updated modelling assumptions

The company summarise updated model assumptions in Table 11 of their technical engagement response. We comment on the company's response to the key issues and preliminary scientific judgements from the NICE Technical Team that affect the model in Table 7 below.

Table 7: Modelling issues raised by NICE technical team

Issues and preliminary judgements in NICE Draft Technical Report	*Company revised base case assumptions and scenarios*	*ERG comments*
Issue 2: Generalisability of clinical evidence Most patients with CSCC are closer to 80 than 70. Unclear if this reflects the average age of patients who will receive cemiplimab	Base case: age 70.4 years (mean in cemiplimab studies) Scenarios: - 80 years - [redacted] years (UK review)	Issue regarding age appropriately addressed, although there may be other questions of generalisability that cannot be modelled. Company's scenario analysis shows higher ICERs at older ages (see section 3.6.5 below). This is expected given the use of age-specific population mortality and utility data in the model.
Issue 3: Clinical evidence data source The results of the integrated analysis provide the best available clinical data to inform the base case	Base case: integrated data from the phase I study and groups 1 and 2 from the phase II (groups 1 and 2 only), [redacted] data Scenarios: - phase II only (groups 1 & 2) - phase II only (groups 1-3) - phase I and II (groups 1-3)	Issue appears to have been appropriately addressed but ERG cannot replicate scenario results (PFS and OS functions used in scenarios are not reported). Company reports that with the updated analysis: ICERs are similar for the integrated and phase II only scenarios; and that scenarios including the fixed dose (group 3) have lower ICERs than scenarios based on weight-based dosing alone.
Issue 4: Quality of evidence for chemotherapy and BSC **Issue 5: Validity of indirect treatment comparisons**	Base case: Jarkowski data for chemotherapy and BSC (naïve comparison) Scenarios: STC adjustment; EGFR inhibitor proxy for BSC	Not addressed. Efficacy data from UK retrospective case note review expected to be available in [redacted] and incorporated in ITC and model by [redacted]. See 3.5 above.

Issues and preliminary judgements in NICE Draft Technical Report	*Company revised base case assumptions and scenarios*	*ERG comments*
Issue 6: clinical plausibility of extrapolated overall survival	Cemiplimab: OS and PFS curves revised based on [redacted] data cut. Comparators: no change to base case. Exploratory scenario with fixed hazard (exponential) to achieve mean survival of 1 year in control arms (based on clinical opinion at TE teleconference), compared with [redacted] years in base case.	The company's 1 year mean survival scenario (37% survival at 1 year and 0.7% at 5 years) reduces the ICER estimate for chemotherapy. ERG could not replicate the reported result of this scenario for the BSC comparator. We note high uncertainty over the 1 year scenario, as it is not based on observed data and assumes a constant hazard.
Issue 7: Treatment duration (stopping rules)	Base case assumes treatment cap of 24 months for cemiplimab and mean of 3 treatment cycles for chemotherapy Scenarios with 22 month and no stopping rule for cemiplimab	Issues appropriately addressed. ICERs are lower with a treatment cap of 22 months assumed for cemiplimab: and higher if no treatment cap is applied.
Issue 8: Persistence of treatment benefits The NICE Technical Team prefer the more conservative estimate of 3 years for treatment effects	Base case assumes 3 year persistence of benefits after stopping cemiplimab (hazard relative to chemotherapy set to 1 after this time) Scenarios of 3 and 5 year persistence of benefits combined with 22 month, 24 month, and no stopping rule	Issue is appropriately addressed. The company shows that ICERs are lower for scenarios with 5 year treatment benefits compared with equivalent scenarios with 3 year treatment benefits
Issue 9: Adverse events costs and effect The Technical Team prefer annual recurrence of AE cost and QALY loss for duration of treatment effects and equal AE QALY loss and costs for chemotherapy	No change: one-off impact of AEs with higher AE-related costs and QALY loss for cemiplimab than for chemotherapy They company notes that the one-off approach reflects the views of clinical experts at the technical engagement teleconference.	The company does not incorporate the technical team's preliminary preferences in their base case or scenario analysis. For completeness, we report scenario analysis to reflect uncertainty over late-onset AEs in section 3.6.6 below, although this has a small impact on ICERs.

Issues and preliminary judgements in NICE Draft Technical Report	*Company revised base case assumptions and scenarios*	*ERG comments*
Issue 10: Resource use prior to progression	ERG's estimates for this health state	Issue is appropriately addressed.
Other changes to model		
Choice of survival functions for cemiplimab PFS/ OS extrapolations	The company base case uses lognormal functions for cemiplimab OS and PFS, based on lowest DIC with decreasing hazards. No scenario analysis	See section 3.3 above regarding the revised cemiplimab OS/ PFS curves. We note uncertainty over the choice of survival functions that is not reflected in the company's technical engagement response. See section 3.6.6 below for ERG scenario analysis.
Health state utility estimates	Updated based on EORTC-QLQ30 in phase II [redacted] data cut, mapped to EQ-5D-3L using Longworth mapping. See section 3.4 above.	The update has a favourable effect on the ICERs because the smaller estimated decrement for progression increases modelled post-progression utility, increasing the projected QALY gain from improved survival. See ERG analysis in section 3.6.6.

3.6.2 Appendix F.2. Fixed dose adjustment

In their revised model, the company include an option to adjust the PFS and OS curves for cemiplimab to estimate outcomes with a fixed 350mg dose of cemiplimab, in order to reflect the anticipated market authorisation. If selected, the model applies hazard ratios of [redacted] and [redacted] to fitted survival functions for PFS and OS, respectively. It is stated that the adjustments are based on differences between outcomes in the weight-based dose and fixed dose groups in the phase II study ([redacted] data), but no details are given about the method of estimation. In particular, it is not stated whether or how estimates are adjusted for other differences between the weight-based groups (metastatic and locally advanced CSCC) and the fixed dose group (metastatic disease only).

The company report a scenario with the fixed dose adjustment applied to their revised base case, which uses PFS and OS curves fitted to weight-based data only (integrated phase I and phase II groups 1 and 2, [redacted]). This reduces ICER estimates for cemiplimab relative to both comparators (see 3.6.5 below).

However, the ERG considers that this analysis further highlights uncertainty over the cost-effectiveness of cemiplimab. The wide confidence intervals around the fixed-dose adjustment hazard ratios reflect the paucity of data for the fixed-dose group in particular. We conclude that it is not currently possible to assess whether fixed dose cemiplimab is associated with better or worse survival outcomes than weight-based dosing.

3.6.3 Appendix F.3. Hypothetical scenario of mean survival set at 1 year

To reflect clinical expert views at the NICE TE teleconference, the company conducted a hypothetical scenario assuming a mean survival of 1 year in current UK practice. This produces estimates of 37% survival at 1 year and 0.7% at 5 years. The company have appropriately incorporated this in the model for chemotherapy by applying an exponential OS function, with the hazard calibrated to give a mean of 1 life year (undiscounted). As expected, this scenario reduces the ICER estimate for cemiplimab compared with chemotherapy. We note that this estimate is subject to high uncertainty, as it is not based on observed data and assumes a constant hazard. Although the company also reports an ICER compared with BSC for this one-year survival scenario, the ERG has not been able to replicate this.

3.6.4 Appendix F.4. Updated base case cost-effectiveness analysis results

The company present their revised base case estimates of cost-effectiveness in Tables 12 and 13 (company Appendix F.4). The estimated ICER is £45,693 per QALY gained compared with chemotherapy and £47,463 compared with best supportive care (deterministic, with proposed CAA price for cemiplimab).

The ERG replicated the company's base case calculations. We show the impact of revisions to the data and assumptions in the company's base case compared with their original submitted analysis with ERG corrections in Table 8 below. Revisions to the PFS and OS curves and health state utility estimates from the [redacted] data update of the phase II cemiplimab study have the effect of decreasing the ICERs, as does the assumption of reduced use of healthcare resources after progression. Conversely, increasing the maximum duration of cemiplimab treatment from 22 to 24 months, and assuming that on average patients on chemotherapy will only have 3 cycles of treatment, increase the incremental cost, and hence the ICERs.

Table 8 Impact of company's changes to ERG-corrected original base case (deterministic, with proposed CAA price for cemiplimab)

Alteration	Intervention	Total cost	Total QALYs	Pairwise ICERs	ICER change
Original company base case (ERG corrected) *	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	**£49,155**	-
	BSC	[redacted]	[redacted]	**£52,539**	-
PFS & OS from [redacted] update (log-normal)	*Cemiplimab*	[redacted]	[redacted]	-	
	Chemo	[redacted]	[redacted]	£47,129	-£2,026
	BSC	[redacted]	[redacted]	£50,240	-£2,299
Updated utility estimates ([redacted])	*Cemiplimab*	[redacted]	[redacted]	-	
	Chemo	[redacted]	[redacted]	£46,681	-£2,474
	BSC	[redacted]	[redacted]	£49,887	-£2,652
24 month stopping rule	*Cemiplimab*	[redacted]	[redacted]	-	
	Chemo	[redacted]	[redacted]	£51,108	£1,953
	BSC	[redacted]	[redacted]	£54,498	£1,959
3 cycles of chemotherapy	*Cemiplimab*	[redacted]	[redacted]	-	
	Chemo	[redacted]	[redacted]	£50,498	£1,343
	BSC	[redacted]	[redacted]	£52,539	£0
Reduced resource pre-progression	*Cemiplimab*	[redacted]	[redacted]	-	
	Chemo	[redacted]	[redacted]	£47,038	-£2,117
	BSC	[redacted]	[redacted]	£50,415	-£2,124
Revised company base case (cumulative impact)	*Cemiplimab*	[redacted]	[redacted]	-	
	Chemo	[redacted]	[redacted]	**£45,693**	-£3,462
	BSC	[redacted]	[redacted]	**£47,463**	-£5,076

* ERG report Table 35

3.6.5 Appendix F.5. Scenario analyses from the updated cost-effectiveness model

The company report a range of scenario analyses to reflect the discussion during NICE technical engagement teleconference (see Table 14, company Appendix F.5).

The ERG replicated results from all the scenario analyses, with the following exceptions:

- Alternative data sources for cemiplimab PFS and OS (survival functions not reported)
    - Phase II only (groups 1 and 2) naïve comparison
    - Phase II naive, groups 1-3
    - Integrated phase I and II (groups 1-3
- Survival extrapolation for hypothetical scenario with mean OS of 1 year for EGFR comparator (couldn't run in model)

3.6.6 ERG additional scenario analysis

Table 9 Additional ERG scenarios based on revised company base case
(deterministic, with proposed CAA price for cemiplimab)

Alteration	Intervention	Total cost	Total QALYs	Pairwise ICERs	ICER change
Revised company base case	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	**£45,693**	-
	BSC	[redacted]	[redacted]	**£47,463**	-
Functions for extrapolation of PFS and OS					
PFS for cemiplimab Weibull	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	£46,019	£327
	BSC	[redacted]	[redacted]	£47,791	£328
PFS for cemiplimab FP (P1=0, P2=-1)	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	£45,499	-£194
	BSC	[redacted]	[redacted]	£47,264	-£199
OS for cemiplimab Weibull	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	£46,886	£1,194
	BSC	[redacted]	[redacted]	£48,738	£1,275
OS for cemiplimab FP (P1=0, P2=-1)	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	£43,500	-£2,193
	BSC	[redacted]	[redacted]	£45,122	-£2,341
Impact of adverse events for cemiplimab					
Annual recurrence for duration of effects (3 years)	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	£45,965	£272
	BSC	[redacted]	[redacted]	£47,737	£274
Cost and QALY loss due to AEs same as for chemotherapy	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	£45,933	£240
	BSC	[redacted]	[redacted]	£47,708	£245
Annual recurrence with cost and QALY loss same as chemo	*Cemiplimab*	[redacted]	[redacted]	-	-
	Chemo	[redacted]	[redacted]	£46,567	£874
	BSC	[redacted]	[redacted]	£48,351	£887

3.7 ERG comments on company Appendix G (BSC OS data from Sun et al. 2019)

The company have summarised the recently-published study by Sun et al. 2019 which provides OS data for a small (n=20) subgroup of patients with advanced CSCC who were not amenable to curative therapy and received BSC. The company were unable to include any results from this study in their economic analyses within the timeframe available for this technology appraisal. We note that the Sun et al. 2019 study has several limitations similar to those of the Jarkowski et al. 2019 chemotherapy comparator study: it was on a non-UK population (USA); was retrospective (so potentially at risk of selection bias); and the sample size for the relevant subgroup is very small. The company has provided a visual comparison

of the OS curve from Sun et al. 2019 against OS curves from the Jarkowski et al. 2016 study, pooled EGFR inhibitor studies (used as a proxy for BSC in the original CS), and the combined cemiplimab phase I and phase II studies (Figure 14 in company Appendix G). It is unclear whether the cemiplimab data in this Figure includes the fixed-dose group. The Figure shows that median OS in the Sun et al. 2019 BSC subgroup was lower than in these other studies, at only [redacted] months.

3.8 ERG comments on company Appendix H (updated safety data)

The company have presented data on patients' exposure to cemiplimab and on the frequencies of adverse events up to the data cut in [redacted]. In Table 10 below we compare the duration of exposure to cemiplimab at the updated data cut (from Table 16 in company Appendix H) with the duration of exposure reported at the original October 2017 data cut for the safety analysis set. The safety analysis set is defined as all patients in the phase I and phase II studies, including the fixed-dose group, who received at least 1 dose of cemiplimab on or before the defined cut-off date for each study (CS section B.2.10). The updated safety analysis set contains 56 more patients than the original analysis, with an increase in the mean duration of cemiplimab exposure from [redacted] to [redacted] weeks (Table 10). A comparison can also be made for a wider safety population, which is referred to as "Pool 2" in the original submission, and represents all patients who received cemiplimab monotherapy, of any dose, and with any solid tumour apart from hepatocellular carcinoma (HCC) (CS Appendix F).

Table 10 Duration of exposure to cemiplimab, weeks

Analysis	Pool 2 (all monotherapy patients, various tumours excluding HCC)		Safety analysis set (all phase I + phase II study patients)	
Original analysis	Mean: [redacted] [a] Median: NR	N=240	Mean: [redacted] [b] Median: NR	N=163
Updated analysis	Mean: [redacted] Median: [redacted]	N=297	Mean: [redacted] Median: [redacted]	N=219

[a] From CS Appendix Table 18. NR: not reported
[b] From CS Table 11.

In the updated safety analysis set [redacted]% of patients (N=219) experienced at least one Grade ≥3 treatment-emergent adverse event (TEAE), as compared to [redacted]% (N=163) in the original analysis (based on data from CS Appendix Table 17). In the updated safety set analysis [redacted]% of patients experienced at least one serious TEAE; [redacted]% experienced at least one

treatment-related serious TEAE; [redacted]% experienced at least one immune-related adverse event; [redacted]% experienced at least one Grade ≥3 immune-related adverse event; and 7.3% experienced permanent treatment discontinuation due to a TEAE. No new fatal TEAEs occurred between the analysis reported in the CS and the [redacted] data cut.

Rates of specific adverse events cannot be compared directly between the updated and original analyses due to differences in how the reported safety results were defined. However, the overall types and rates of individual events observed up to the [redacted] data cut appear similar to those reported in the original CS. The only Grade ≥3 TEAE that affected at least 5% of patients in the updated safety analysis set were anaemia and fatigue (both reached [redacted]%, in the 350mg q3w fixed-dose group).

Overall, the updated data provided by the company for the safety analysis set and the wider Pool 2 safety population do not appear to signal any new safety issues.

4 ERG conclusion

The ERG believes that, subject to some issues discussed above, the company's updated analyses generally make the best use of the currently available data on cemiplimab, chemotherapy and BSC, and addresses most of the concerns raised by NICE. However, the updated analyses do not resolve the fundamental uncertainties in the ITC methods that stem from the small size of the comparator chemotherapy study (N=18) (Jarkowski et al. 2016) and the lack of data to enable adjustment of prognostic factors. Future analyses, which the company expects to provide in [redacted], may help to reduce some of these uncertainties.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report – updated after technical engagement

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)

1. Summary of the post-engagement technical report

1.1 This document is the post-engagement version of the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The post-engagement technical report used by the appraisal committee to help it make decisions at the appraisal committee meeting. A draft version of this technical report was sent out for consultation between 12th February and 12th March 2019. The draft report included a list of issues that have an impact the certainty of the company's estimates of clinical or cost effectiveness. The aim of the consultation was to seek feedback from consultees and commentators on these issues to help inform the technical team's preferred modelling assumptions.

Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements of the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the key evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. The issues that were considered at technical engagement are described in detail in section 2 below, along with the feedback that was received. The following table summarizes the current status of each issue in terms of the technical team's view on the level of outstanding uncertainty.

Table 1: Issue status following technical engagement

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 1 – Definition of the patient population and appropriate comparator(s)	The clinical profile of patients with advanced CSCC and whether there were clinical differences between patients who might be eligible for treatment with cemiplimab and its comparators	Feedback during engagement was consistent confirming both the clinical profile of patients who will be eligible for treatment with cemiplimab (detailed below) and that chemotherapy and best supportive care are both relevant comparators	Level of outstanding uncertainty = low

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 2 – Generalisability of the clinical evidence for cemiplimab	The average age of patients with advanced CSCC and whether the patients that were enrolled in the studies that informed the clinical effectiveness estimates for cemiplimab are representative of the UK population with advanced CSCC	There is still some uncertainty about whether the baseline age of the cohort in the model is appropriate. It remains unclear whether the outcome data from patients in the cemiplimab trials who received the weight-based dose will be in the same as for those who receive the fixed dose in practice	Level of outstanding uncertainty = high
Issue 3 – Clinical evidence data source (Integrated analysis or Phase II only)	Whether pooling data from the phase I and II cemiplimab trails is appropriate	Feedback during engagement was consistent confirming that pooling the phase I and II studies is appropriate	Level of outstanding uncertainty = low

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 4 – Quality of the evidence for chemotherapy and best supportive care	Whether the company's assumption that best supportive care (BSC) is as clinically effective as chemotherapy conservative; whether patients in the Jarkowski et al. 2016 study representative of patients being treated with chemotherapy or BSC in the NHS and if this is the best available evidence for decision making	Feedback during engagement consistently confirmed the company's approach of assuming BSC is as effective as chemotherapy is conservative. The limitations with the Jarkowski 2016 study were also agreed, however, it was also confirmed that there is no other data currently available that would provide a more suitable basis for decision making	Level of outstanding uncertainty = high

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 5 – Validity of the company's indirect comparison and value of further comparator data	Whether it appropriate to use the naïve comparison to inform the estimate of cost effectiveness of cemiplimab; the status of Sanofi's ongoing retrospective chart review study is and what uncertainties in the current analysis it is likely to solve	The naïve comparison provides a potentially conservative estimate of relative effectiveness but the results for the chemotherapy/BSC arm lack validity because modelled the survival benefit does not align with clinical practice; it is still unclear whether using data from Sanofi's retrospective chart review instead of the Jarkowski study would provide a more certain estimate of relative treatment effect of cemiplimab	Level of outstanding uncertainty = high

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 6 – Clinical plausibility of the extrapolated overall survival	Whether the company's survival extrapolations are clinically plausible; whether Merkel cell carcinoma a reasonable proxy for advanced CSCC in terms of predicting overall survival	Feedback consistently confirmed that the chemotherapy extrapolations are implausible but also that the current estimates are optimistic (meaning the cost effectiveness results are likely to be conservative). It was also consistently confirmed that Merkel cell carcinoma was not a reasonable proxy and that the cemiplimab extrapolations are plausible.	Level of outstanding uncertainty = high
Issue 7 – The maximum duration of treatment (the treatment stopping rule)	Whether a stopping rule would be implementable in practice; what the most appropriate stopping rule would be	Feedback during engagement confirmed the technical team's initial preferred assumption of a 24-month stopping rule is reasonable and the company incorporated this into their updated model, but clinical experts noted that a stopping rule may be difficult to implement in practice	Level of outstanding uncertainty = high

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 8 – Persistence of treatment benefits	How long the effect of cemiplimab will last (including whether it will wane over time); whether further data will help reduce uncertainty around the persistence of treatment effects	Feedback during engagement confirmed the technical team's initial preferred assumption of 3-year treatment benefit is reasonable and the company incorporated this into their updated model but this assumption remains uncertain because the trial data are immature	Level of outstanding uncertainty = high
Issue 9 – Adverse events costs and effect	If cost and utility loss due to adverse events is likely to have been underestimated in the company model	Feedback during engagement confirmed that the company's original approach to modelling adverse events was reasonable so their decision not to revise the assumptions in their updated analysis is acceptable	Level of outstanding uncertainty = low
Issue 10 – Resource use in the pre-progression health state	If the company's original estimates of resource use in the pre-progression health state reflect routine NHS practice	Feedback during engagement confirmed that ERG's estimates for pre-progression resource use are more reflective of clinical practice and the company incorporated this into their updated model	Level of outstanding uncertainty = low

Issue title and number	Issues identified pre-engagement	Response to consultation	Issue status following engagement
Issue 11 – End of Life	The current life expectancy of the relevant patient population; if the estimates of survival benefit are robust	Feedback during engagement confirmed that life expectancy with current treatment is likely the be less than 2 years, but this is not reflected in the current chemotherapy extrapolations; it is unclear whether the estimates of the extension to life are sufficiently robust for the end of life criteria to be taken into consideration	Level of outstanding uncertainty = high
Issue 12 – Cancer Drug Fund	What additional value can further data collection provide in terms of clarity around the comparative effectiveness of cemiplimab in the relevant patient population	Data collection in the CDF is unlikely to resolve key uncertainties related to the ITC; meaningful data on the efficacy cemiplimab are unlikely to be available until [redacted]	Level of outstanding uncertainty = high

1.3 Prior to technical engagement the technical team noted that the following issues also have an impact on the company's estimates of clinical and cost effectiveness. However, the technical team did not seek feedback on these points specifically because it was recognised that consultation comments were unlikely to resolve these uncertainties:

- The clinical trial evidence is based on small patient numbers (n=149).

- The clinical trial evidence is immature; median overall survival has not been met.

1.4 The cost-effectiveness results include a commercial arrangement (commercial access agreement) for cemiplimab

1.5 Following the updates the company made to their analysis at technical engagement, the most plausible ICER ranges (based on the current, limited clinical evidence) are as follows:

- Versus chemotherapy: £43,979 to £62,332 per QALY gained
- Versus BSC: £45,745 to £64,146 per QALY gained

  These ranges take account of uncertainty regarding the duration of treatment and the starting age of the patient cohort in the economic model. Because of the limitations in the evidence base, these ICERs are highly uncertain.

1.6 It is unclear if the end-of-life criteria should be considered due to the uncertainty of the modelled survival benefit (see issue 11).

1.7 The technology is unlikely to be considered innovative (see table 3).

1.8 No equality issues were identified.

2. Key issues for consideration

Issue 1 – Definition of the patient population and appropriate comparator(s)

Background/description of issue	- Cemiplimab might not be a suitable treatment for all patients with advanced CSCC who are not candidates for surgery (the population in the draft marketing authorisation) because: • There are a number of potential toxicities associated with the use of cemiplimab • The draft summary of product characteristics includes a number of special warnings that should be considered before prescribing cemiplimab to patients with specific conditions - According to information provided by the NCRI-ACP-RCP: • Many patients with metastatic CSCC are immunosuppressed solid organ transplant recipients (SOTR). Cemiplimab treatment may be too high risk for these patients because it is likely to lead to rejection of their allograft (recipients of kidney transplants may be an exception because they can receive dialysis) • Potentially serious immunologically-based adverse effects can be expected in about 15% of patients receiving cemiplimab, leading to drug withdrawal in about 7%.
Why this issue is important	- It is important to understand who will benefit from cemiplimab, their characteristics and those for whom the technology will not be suitable.
Questions for engagement	a. What is the clinical profile of patients in England with advanced CSCC? b. Are there any important clinical differences between patients who might be eligible for treatment with cemiplimab/chemotherapy/best supportive care (BSC)? c. What clinical characteristics might mean that treatment with cemiplimab is not appropriate?

Technical team preliminary scientific judgement and rationale	- The technical team was unable to ascertain the clinical profile of patients with advanced CSCC nor comment on the clinical differences between patients who might be eligible for treatment with cemiplimab and its comparators – clinical opinion would be valued in resolving these areas of uncertainty. - It was unclear what characteristics might mean that treatment with cemiplimab is not considered appropriate, however, the following may be relevant: • Frailty which might make cemiplimab's potential toxicities intolerable • Previous solid organ transplant (with possible exception of kidney transplant) • Ongoing or recent auto-immune disease or treatment with immunosuppressive drugs • Clinical opinion would be valued in determining whether these or any other characteristics are important
Summary of comments	- Comments received from clinical experts: • Most patients in England with advanced CSCC are elderly (and often frail) or immunosuppressed. There will be some (rare) younger immunocompetent patients. PD-1 inhibitors are much better tolerated than chemotherapy in an elderly population (it is expected that there will be patients for whom cemiplimab is appropriate, but chemotherapy is not). Cemiplimab is not appropriate for solid organ transplant recipients, nor for some patients with a history of significant autoimmune disease. BSC may be the only appropriate treatment for very frail elderly patients (that is, cemiplimab would not be considered for patients with ECOG status 3 or 4) - Comments received from company (Sanofi): • There is limited evidence on the clinical profile of patients in England with advanced CSCC but clinical experts have indicated that they are often elderly and frail. Approximately 1/3 of patients are immunocompromised, of which most will have had a solid organ transplant with the majority being recipients of kidney transplants. The remainder of immunocompromised patients will likely have either autoimmune disease (such as rheumatoid arthritis or inflammatory bowel disease), chronic lymphocytic leukaemia or viral infection (HIV or Hepatitis B/C). Clinical experts anticipate that cemiplimab would displace the use of chemotherapy in advanced CSCC and a significant proportion of patients currently on BSC would be eligible for treatment with cemiplimab. Clinical experts have advised that patients who are severely immunocompromised would not be suitable for treatment

	with cemiplimab (in particular patients with a solid organ transplant because of the elevated risk of graft rejection), nor will cemiplimab be considered for frail patients with poor performance status. Patients with these characteristics were excluded from the key trial in the company's analysis - ERG considerations: • The company has not provided any new information. Their responses are consistent with their original submission and concur with the opinions of clinical experts
Technical team scientific judgement after engagement	- It has been consistently stated that: • Most patients with advanced CSCC in England are elderly and frail • Patients with the following clinical characteristic are unlikely to be eligible for treatment with cemiplimab: ▪ history of solid organ transplant ▪ significant autoimmune disease ▪ ECOG performance status higher than 2 • Cemiplimab is likely to be considered an appropriate treatment alternative for many of the patients who currently receive chemotherapy. It is also likely to be considered an appropriate treatment for some patients who currently receive BSC. Therefore, chemotherapy and BSC are both relevant comparators.

Issue 2 – Generalisability of the clinical evidence for cemiplimab

Background/description of issue	- The clinical effectiveness estimates in the company's economic model are informed by the data from two ongoing, non-comparative 'phase I' and 'phase II' studies with relatively small sample sizes (total N=108): • The ERG commented that the populations of the included cemiplimab studies are younger and fitter than the anticipated UK clinical population for whom cemiplimab would be indicated • European family origin, exposure to UV radiation (especially in people with fair skin), history of solid organ transplant and use of immunosuppressive drugs are cited as risk factors for the disease (CS section B.1.3, p16). However, neither of the cemiplimab trials included any patients from the UK (studies were conducted in locations that have a different ethnic mix to the UK and where patients may have received greater exposure to UV radiation) - In addition, the patients in the cemiplimab trials received a weight-based dose of cemiplimab but it is anticipated that the marketing authorisation will specify a fixed-dose regimen: patients receiving a fixed dose may have different outcomes to the patients who received a weight-based dose (for example, adverse event rates may differ)
Why this issue is important	- Understanding to what extent the patients and interventions in the studies are representative of the population is an important aspect and needs to be taken into account when considering whether the evidence presented by the company is acceptable for decision making. - ERG scenario analysis shows that varying the baseline characteristics of the patients in the company's economic model results in big changes to the ICERs
Questions for engagement	a. What is the average age of patients with advanced CSCC? b. Are the patients that were enrolled in the studies that informed the clinical effectiveness estimates for cemiplimab representative of the UK population with advanced CSCC?
Technical team preliminary scientific judgement and rationale	- The technical team recognises that the advanced CSCC population in the UK is likely to be heterogeneous. The technical team take the view that most patients with advanced CSCC are likely to be closer to 80 than 70 years old but it's uncertain if this reflects the average age of the patients that will received cemiplimab (see issue 1)

Summary of comments	- Comments received from clinical experts: • Most patients in England with advanced CSCC are aged between 70-90 years but age is less important than frailty in determining eligibility for treatment with cemiplimab. The patients in the cemiplimab trials are representative of the UK patient population. There may be some rare cases where patients are significantly younger if they have a genetic predisposing risk such as xeroderma pigmentosa or recessive dystrophic epidermolysis bullosa. - Comments received from company (Sanofi): • The mean age of the N=106 patients with advanced CSCC patients in UK clinical practice who are enrolled in Sanofi's ongoing retrospective chart review is [redacted] years, which is consistent with the mean age of 70.4 years from the cemiplimab trials. A recent publication by Sun et al 2019 included a cohort of N=20 immunocompetent patients with CSCC with unresectable lesions; the median age of these patients was 73 years. The age of the population at baseline in the company's base case analysis remains unchanged (70.4 years) but the company has also conducted scenario analyses with this parameter set to [redacted] and 80 years. - ERG considerations: • No new information is presented regarding the representativeness of patients enrolled in studies providing estimates of the clinical effectiveness of cemiplimab • The company report a scenario with the fixed dose adjustment applied to their revised base case, which uses PFS and OS curves fitted to weight-based data only (integrated phase I and phase II groups 1 and 2, [redacted]). This reduces ICER estimates for cemiplimab relative to both comparators. However, the ERG considers that this analysis further highlights uncertainty over the cost-effectiveness of cemiplimab. The wide confidence intervals around the fixed-dose adjustment hazard ratios reflect the paucity of data for the fixed-dose group in particular. The ERG conclude it is not currently possible to assess whether fixed dose cemiplimab is associated with better or worse survival outcomes than weight-based dosing

<table>
<tr><td>Technical team scientific judgement after engagement</td><td>- There is still some uncertainty about whether the baseline age of population in the model is appropriate. Clinical expert opinion indicates that patients who are much older than 70 may potentially benefit from cemiplimab treatment but the company have not updated the age of the patients in their base case (currently matched to the phase II trial population mean age of 70.4). Scenario analyses demonstrate that changing the baseline age of patients in the model has a significant impact on the ICER.
<table>
<tr><th>Age of patients at baseline in economic model</th><th>70.4 years[a]</th><th>71.67 years[b]</th><th>80 years[c]</th></tr>
<tr><td>ICER vs. chemotherapy (£/QALY gained)</td><td>45,693</td><td>46,506</td><td>55,931</td></tr>
<tr><td>ICER vs. BSC (£/QALY gained)</td><td>47,463</td><td>48,324</td><td>58,323</td></tr>
</table>
Bold text indicates company's base case ICERs. [a] mean age of patients in cemiplimab trials; [b] mean age of patients in Sanofi's ongoing retrospective chart review; [c] mid-point in plausible age range for most potential treatment candidates according to clinical experts
- It remains unclear whether the outcome data from patients in the cemiplimab trail who received weight-based dose are likely to representative of the outcomes that will occur using the fixed-base dose that will be available in practice</td></tr>
</table>

Issue 3 – Clinical evidence data source (Integrated analysis or Phase II only)

Background/description of issue	- Some differences are evident between the advanced CSCC populations in the phase I and phase II studies. For example, a [redacted] of phase I than phase II study participants had received prior cancer related systemic therapy, prior cancer related radiotherapy, and [redacted]. There are also differences in baseline characteristics, the exposure to cemiplimab and length of follow-up were longer in the phase I study. - It is unclear how meaningful these relatively small differences (between the advanced CSCC populations in the phase I and phase II studies are given the small sample sizes involved (see Table 4 ERG report page 25). However, the ERG clinical advisors considered that pooling these studies in an 'integrated' analysis was appropriate.

Why this issue is important	- Changes to the clinical data source lead to some large changes in ICERs. Excluding the phase I cemiplimab study data increases ICERs above £60,000 per QALY gained. - Differences are evident between the population in the phase I and phase II studies
Questions for engagement	Is it appropriate to pool the data from the phase I and phase II studies or are the reasons for excluding the phase I study (the differences in baseline characteristics, exposure to cemiplimab, length of follow-up and extent of prior cancer-related therapy) sufficient to exclude the phase I study?
Technical team preliminary scientific judgement and rationale	- A limitation in the clinical effectiveness evidence for cemiplimab is that the sample sizes are small; excluding the phase I participants reduces the sample size further. - The results of the integrated analysis provide the best available clinical data to inform the base-case. - The technical team prefers the pooled data hence the integrated analysis

Summary of comments	- Comments received from clinical experts: • It is appropriate to pool the data from the phase I and II cemiplimab trials. The differences in baseline characteristics are not sufficient to exclude phase I data. - Comments received from company (Sanofi): • It is appropriate to pool the data from the phase I and the phase II cemiplimab trials given the small sample sizes and the fact that the phase I trial provides additional follow up data. However, as the data from the cemiplimab phase II trial matures Sanofi believe that data from this trial alone will become more relevant for decision making. • The company has now supplied an updated model which incorporates data from [redacted]. This incorporates scenario analyses which demonstrate that removing the phase I study data now has a minimal impact on the ICER ▪ ICERs based on integrated analysis of the two trials: £45,693/QALY and £47,463/QALY vs chemotherapy and BSC respectively ▪ ICERs based on phase II trial data only: £45,269/QALY and £47,038/QALY vs chemotherapy and BSC respectively - ERG considerations: • the company stated that as the data from the phase II study mature, this study alone will become "more relevant" for decision making, but they do not provide a justification for this or discuss the implications of excluding the phase I study
Technical team scientific judgement after engagement	- Feedback has consistently indicated that the technical team's initial preference for pooling the studies is acceptable

Issue 4 – Quality of the evidence for chemotherapy and best supportive care

Background/description of issue	- No direct head-to-head studies of cemiplimab against chemotherapy or best supportive care were identified - Only one study of chemotherapy in a relevant advanced CSCC population was eligible (Jarkowski et al. 2016). It is a retrospective chart review conducted in the United States which included 25 patients, of whom only 18 had received relevant platinum-based chemotherapy. - No studies were identified that provided any direct evidence for PFS or OS under BSC. The company base case therefore used the same clinical effectiveness data for both chemotherapy and BSC - The ERG agreed that Jarkowski et al. 2016 appears to provide the best available comparator data for chemotherapy in the advanced CSCC population but note that it has several limitations mainly the small sample size and the potential for bias by virtue of its retrospective design. - The ERG noted it is not possible to draw meaningful conclusions about the cost-effectiveness of cemiplimab for patients who currently receive BSC in the absence of information about their current rates of progression and survival but acknowledged the company's attempts to find alternative sources of information. The ERG also agreed that outcomes for chemotherapy and EGFR inhibitors are not likely to be worse than for BSC alone (so, these proxies should in theory provide conservative ICERs for cemiplimab), but qualified this statement by saying that comparisons based on the available data sources are still highly uncertain, as they rely on small, uncontrolled samples
Why this issue is important	- The survival extrapolations in the economic model for both chemotherapy and BSC are based on the data from the 18 patients who had received relevant platinum-based chemotherapy in Jarkowski et al. 2016
Questions for engagement	a. Is the assumption that BSC is as clinically effective as chemotherapy conservative? If so is it reasonable? b. Are the patients in the Jarkowski et al. 2016 study representative of patients being treated with chemotherapy or BSC in the NHS? c. Given the design of Jarkowski et al. 2016 (retrospective chart review) and the size of the sample (N=18) that ultimately informed the base case survival estimates for both chemotherapy and BSC, is this evidence the best available for decision making?

Technical team preliminary scientific judgement and rationale	- The patients in the study by Jarkowski et al. 2016 are unlikely to be fully representative of the UK population with advanced CSCC - The data that informed the base case survival estimates (N=18) for both chemotherapy is potentially biased because it is unclear how the patients were selected. - The technical team recognises that the company is currently conducting retrospective chart review of patients with advanced CSCC and this may provide better data on the comparator treatments (see issue 6) - The technical team recognises that issues of generalisability are unlikely to be resolved through technical engagement but consider that the committee should take this into account.
Summary of comments	- Comments received from clinical experts: • The assumption that BSC is as clinically effective as chemotherapy is reasonable (although in real life chemotherapy is possibly worse than death for the patient) • The limitations with the Jarkowski study noted prior to engagement are serious; modelling based on this study has given a totally unrealistic overall survival estimates (see Issue 6) • Sanofi's retrospective chart review of UK patients or an audit of UK oncologists who treat this disease would be provide a better basis for decision making - Comments received from company (Sanofi): • The assumption that BSC is as clinically effective as chemotherapy is reasonable and this is supported by clinical opinion, the company's scenario analysis using data from EFGR inhibitor studies and a recent publication (Sun et al 2019) - ERG considerations: • The company refer to existing information in their CS in support of ▪ the assumption that BSC is as clinically effective as chemotherapy, and ▪ that Jarkowski et al. 2016 study currently provides the best evidence to inform comparisons versus chemotherapy and, by proxy, versus BSC • data from the company's ongoing retrospective chart review study are not yet available • the Sun et al. 2019 study has several limitations similar to those of the Jarkowski et al. 2019 chemotherapy comparator study: it was on a non-UK population (USA); was retrospective (so

	potentially at risk of selection bias); and the sample size for the relevant subgroup is very small. The company has provided a visual comparison of the OS curve from Sun et al. 2019 against OS curves from the Jarkowski et al. 2016 study, pooled EGFR inhibitor studies (used as a proxy for BSC in the original CS); the figure shows that median OS in the Sun et al. 2019 BSC subgroup was lower than in these other studies, at only 5.0 months
Technical team scientific judgement after engagement	- Feedback during engagement consistently confirmed the limitations with the Jarkowski 2016 study, but also that there is no other data currently available that would provide a more suitable basis for decision making

Issue 5 – Validity of the company's indirect comparison and value of further comparator data

Background/description of issue	- Comparative effectiveness is very uncertain due to the lack of a randomised control group, and potential confounding of the observational comparisons that is not adequately adjusted for in the simulated treatment comparison (STC) and matched adjusted indirect comparison (MAIC). - Both the STC and MAIC approaches account for inter-study heterogeneity by adjusting the population characteristics of the cemiplimab studies to match those of the chemotherapy study. The ITC could only include two of 12 prognostic covariates identified as potentially important by the company's clinical experts. Both MAIC and STC methods make a fundamental assumption that all effect modifiers and prognostic factors are accounted for in the covariates used. - The company's MAIC and STC methods are consistent with the NICE Decision Support Unit guidance on methods for population-adjusted indirect comparisons. The NICE DSU guidance does not provide any criteria for choosing between STC or MAIC and the ERG consider it appropriate that the company has explored using both approaches. - The company noted that when the results of the MAIC and STC were inputted into the economic model, the survival estimates were more favourable than in the 'naïve comparison' (when parametric curves were fitted directly to the observed data from the integrated analysis of the cemiplimab trials and data from the n=18 patients from Jarkowski et al. 2016). Given the uncertainty in the STC and MAIC results,

	the company decided to use the naïve comparison in their base case with the STC results used in scenario analysis as these were more conservative that the results of the MAIC. - The ERG agrees that the company's approach to the indirect comparison is appropriate, given that direct head-to-head evidence is lacking and that IPD are available for cemiplimab. They note there are considerable limitations to both the MAIC and STC approaches, as follows: • The matching or adjustment will further reduce the already small effective sample size (ESS) for the reference study. • Both methods match to the target study population rather than to an appropriate real-world population (so it is important that the Jarkowski study adequately reflects patients who would present for advanced CSCC therapy in the NHS). • Both methods make a fundamental assumption that all effect modifiers and prognostic factors are accounted for in the covariates used in the MAIC or STC. This is considered 'largely impossible' to meet, leading to an unknown amount of bias in the unanchored estimate. • Clinical advisors suggested that health-related quality of life and use of supportive care is likely to be quite different for people with head and neck squamous cell carcinoma (HNSCC) or melanomas than for those with CSCC, but that Merkel cell carcinoma and basal cell carcinoma are more comparable. - In their responses to the ERG's clarification questions the company noted a retrospective chart review study, conducted by Sanofi, is currently ongoing (anticipated sample size ~600 patients now being recruited in the US and EU, including the UK) and state that, once available, the results of the chart review should provide a more appropriate dataset to base comparisons on (company response to clarification question A11)
Why this issue is important	- The naïve comparison is used for the company's base case. The naïve comparison was selected as being the most conservative analysis (gave least benefit to cemiplimab out of the three approaches to indirect comparisons) rather than being methodologically appropriate. - Naive comparisons are inadvisable as effectiveness outcomes are highly likely to be confounded with population differences between the studies. - PFS and OS distributions were fitted to digitised Kaplan-Meier data from the integrated phase I and phase II cemiplimab studies (naive and STC-adjusted comparisons)

Questions for engagement	a. Given the uncertainty in the STC/MAIC results, is it appropriate to use the naïve comparison to inform the estimate of cost effectiveness of cemiplimab? b. What is the current status of Sanofi's ongoing retrospective chart review study? c. How many patients have been recruited? d. Are any interim results available – if not, why not? e. When is the study likely to be complete? f. Is the population of Sanofi's ongoing retrospective chart review likely to be representative of patients receiving treatment for advanced CSCC in the NHS? g. Will data be available for patients receiving cemiplimab, chemotherapy and best supportive care? h. How would these additional data reduce the key uncertainties in the current STC/MAIC?
Technical team preliminary scientific judgement and rationale	The company's approach to the ITC is appropriate for an analysis attempt given the lack of available data, and the analysis is generally well reported and consistent with NICE DSU guidance. However, the data shortage is serious and imparts major uncertainty to the results obtained from the analyses. The technical team are unclear as to when further data from the ongoing retrospective chart review study, conducted by Sanofi, will become available or whether it will significantly reduce the current uncertainty in the ITC.

<table>
<tr><td>Summary of comments</td><td>
- Comments received from clinical experts:

the naïve comparison can be used to estimate cost effectiveness, additional data could potentially reduce the uncertainties. Sanofi's ongoing retrospective chart review should provide data on chemotherapy and BSC

- Comments received from company (Sanofi):

The naive comparison continues to provide the most conservative estimates of cost effectiveness, so the company have not changed their approach.
Recruitment to Sanofi's retrospective chart review is ongoing (anticipated total population~600), although recruitment of the UK cohort (n=106) is complete and the baseline characteristics are now available (see table 10 of company's technical engagement response appendix).

Detailed timelines on the data availability and incorporation of the chart review study data in the ITC and the economic model
<table>
<tr><th>Action</th><th>Date</th></tr>
<tr><td>Availability of the chart review data from the UK cohort including OS and PFS curves</td><td>[redacted]</td></tr>
<tr><td>Integration of UK chart review data into the ITC</td><td>[redacted]</td></tr>
<tr><td>Integration of UK chart review analysis results into the CEA</td><td>[redacted]</td></tr>
<tr><td>Availability of the chart review data from US and Europe including OS and PFS curves</td><td>[redacted]</td></tr>
<tr><td>Integration of US and European chart review data into the ITC</td><td>[redacted]</td></tr>
<tr><td>Integration of US and European chart review analysis results into the CEA</td><td>[redacted]</td></tr>
</table>

Patients treated for advanced CSCC in the NHS should be well represented because these data were collected across [redacted] UK sites
Data captured will not include records of treatment with cemiplimab; it will, however, include chemotherapy and BSC although BSC will reflect clinical practice in the respective country

</td></tr>
</table>

	• The retrospective chart review study will provide an alternative dataset to Jarkowski, the availability of the individual patient-level data (IPD) from this study alongside IPD from the cemiplimab trial will allow for more prognostic factors to be adjusted for and thus a more meaningful indirect treatment comparison (ITC) - ERG considerations: • The company have updated their analysis at technical engagement but it still relies on the naive comparison so it is still highly uncertain. • Incorporating data from Sanofi's retrospective chart review study in future may reduce some of the uncertainty in the STC/MAIC because: ▪ the sample size in the ITC analyses would be larger which has the potential to reduce statistical uncertainty ▪ the population would be more reflective of a real-world UK population, this would reduce clinical uncertainty ▪ aggregate baseline characteristics data provided by the company suggest that at least 5 prognostic factors would be available in both the retrospective chart review and the cemiplimab integrated (or phase II study) analyses that could be considered for statistical adjustment, reducing decision uncertainty • The ERG notes the following issues with Sanofi's retrospective chart review ▪ It covers a population that was sampled during 2011-2015. The ERG is unclear why the data are not yet available, more than three years after sampling ended ▪ It includes UK patients and the eligibility criteria that are consistent with the company's decision problem (so patients included should be representative of patients receiving treatment for advanced CSCC in the NHS) but the company has not reported the process for selection of the sites so it is unclear where these were located, how the sites/oncologists were recruited (e.g. whether any incentives were involved), and whether there were any relevant sites/oncologists that were not selected ▪ It is also unclear what the length of follow-up was for patients included in the retrospective chart review

	▪ Some differences are evident between the baseline characteristics of patients included in the retrospective chart review and those included in the cemiplimab integrated analysis (see section 3.5 of the ERG response to the company's technical engagement response appendix)
Technical team scientific judgement after engagement	- Uncertainties identified pre-engagement have not been fully resolved. Specifically, it remains unclear whether using the naïve comparison to inform the cost effectiveness estimates is appropriate because the modelled the survival benefit for the chemotherapy/BSC arm does not align with clinical practice (see issue 6). - It also remains unclear whether using data from Sanofi's retrospective chart review instead of the Jarkowski study would provide a more certain estimate of relative treatment effect because: • Clinical opinion is needed to understand whether ▪ the baseline characteristics of the patients in the UK cohort of the retrospective chart review are representative of the population who are likely to receive treatment ▪ data from the UK cohort or the entire study population would provide the most robust basis for analysis • The ERG have noted that 5 prognostic variables could potentially be controlled for in a future STC or MAIC analysis, however, this still leaves 7 out of the 12 variables and it is unclear how much uncertainty would remain • A major limitation of any STC or MAIC of single arm studies is the inherent assumption that all prognostic and effect modifying variables are accounted for – this assumption is implausible. Moreover, the level of uncertainty in the results arising from the inability to adjust for unidentified prognostic/effect modifying variables is difficult to quantify. These issues are of concern for this analysis because: ▪ of the limitations in the evidence used to identify the original 12 prognostic variables ▪ the difference in the study designs (single-arm controlled intervention studies vs. retrospective observational study) increases the likelihood of unknown prognostic variables being an issue • Much of the current uncertainty in the results is due to the immaturity of the cemiplimab trial data. Changes to the comparator data/approach to ITC will not reduce this uncertainty

Issue 6 – Clinical plausibility of the extrapolated overall survival

<table>
<tr><td>Background/description of issue</td><td>- The issue is not the extrapolation of overall survival but the clinical plausibility of the extrapolations.
- The survival estimates which inform the company's ICERs are uncertain because:
• The data used to fit PFS and OS curves for cemiplimab (the integrated analysis of the phase I and phase II studies [n=108]) are immature.
▪ At a median follow-up of 8.92 months, median progression-free survival, PFS, was not reached. The estimated 12-month PFS was [redacted] (95% CI [redacted] to [redacted] in the integrated analysis (phase I study [redacted] phase II study [redacted] Median overall survival, OS, was also [redacted] in either study. Estimated 12-month survival was [redacted](95% CI [redacted] to [redacted] in the integrated analysis and was similar across studies.
• There are serious limitations with the data used to fit PFS and OS curves for the comparators arms of the model
- The ERG described the company's approach to extrapolation as 'well-structured' and the company's choice of base case PFS and OS distributions as 'reasonable'.</td></tr>
<tr><td>Why this issue is important</td><td>- The results of the cost effectiveness analysis are sensitive to changes in OS extrapolations</td></tr>
<tr><td>Questions for engagement</td><td>a. How clinically plausible are the company's current base-case estimates of overall survival?
<table><tr><th>Treatment</th><th>OS at 5 years</th><th>OS at 10 years</th></tr><tr><td>Cemiplimab</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Chemotherapy/BSC</td><td>[redacted]</td><td>[redacted]</td></tr></table>
b. Is Merkel cell carcinoma a reasonable proxy for advanced CSCC in terms of predicting overall survival (as suggested by the ERG)?</td></tr>
</table>

Technical team preliminary scientific judgement and rationale	- The company fitted a wide range of functional forms to extrapolate PFS and OS and followed recommended methods to select distributions for their base case and scenarios. They appropriately restricted consideration to distributions that continue to decline, rather than those that plateau. Therefore the technical team has included the company's chosen extrapolations in the preferred base case. - Results of the indirect treatment comparisons suggest that cemiplimab improved OS and PFS when compared to platinum-based chemotherapy. However, both the company and ERG agree that due to limitations of the analyses these results are highly uncertain, precluding any meaningful conclusions. - The technical team would like clinical opinion on the plausibility of the survival extrapolations in both arms of the current base-case.
Summary of comments	- Comments received from clinical experts: • The cemiplimab survival estimates are plausible although the data are too immature to confirm currently. Learning from other PD-1 inhibitors, we might expect to see a long tail in the response arm. Whether this will be at 40% or 20% is not known and clearly makes a big difference to overall survival. • The chemotherapy/BSC estimates appear much too optimistic. Experience in clinical practice suggests there will be very few (if any) patients alive at 5 or 10 years. Data presented in a recently published study by Sun et. al 2019 supports this anecdotal evidence; the study reported the median survival time for n=36 patients locally recurrent or metastatic CSCC (on the head and neck) who were not suitable for salvage surgery as 4.7 months (none were alive by 6 months). • Merkel cell carcinoma is not a reasonable proxy for advanced CSCC in terms of predicting overall survival. - Comments received from company (Sanofi): • Sanofi's comments align with those of the clinical experts. The company note that the overestimation of survival in the chemotherapy arm mean that their base case results are conservative and this is supported by scenario analysis that was conducted where survival of patients on chemotherapy is set to 1 year (ICERs for this scenario were lower than the base case ICERs, see table 14 of company's technical engagement response appendix)

	- ERG considerations: • The company's 1 year mean survival scenario (37% survival at 1 year and 0.7% at 5 years) reduces the ICER estimate for chemotherapy but ▪ The ERG could not replicate the reported result of this scenario for the BSC comparator. ▪ It is highly uncertain, as it is not based on observed data and assumes a constant hazard
Technical team scientific judgement after engagement	- This issue requires discussion at the AC because clinical opinion has consistently indicated that: • the cemiplimab extrapolations are plausible • the chemotherapy/BSC extrapolations are implausible but confirmed the current estimates are optimistic (meaning the cost effectiveness results are likely to be conservative) - The implausibility of the chemotherapy/BSC extrapolations needs to be viewed in the context of the limitations in the underlying data for these comparators (see issue 4) and the naïve ITC (see issue 5) and may influence decision-making regarding the applicability of the end-of-life criteria (see issue 11)

Issue 7 – The maximum duration of treatment (the treatment stopping rule)

Background/description of issue	- The company assumed in the model for cemiplimab, treatment duration was equal to progression-free survival (PFS) or 22 months (whichever came first) - Protocols for the cemiplimab studies placed limits on the duration of treatment (CS Table 4). - Changes to the maximum duration of treatment has an impact on the ICER. The direction of the impact (whether it drives the ICER up or down) and whether the change is big or small is moderated by how long the cemiplimab treatment benefit is assumed to persist (see issue 8). For example, the ERG conducted a scenario analysis where the maximum duration of treatment was set to 1 year and the treatment benefit was assumed to last for 2 years in total – this resulted in ICERs below £50,000 per QALY. In another scenario the ERG removed the stopping rule and assumed the treatment benefit would last for 3 years in total – this resulted in ICERs above £69,000 per QALY - The ERG view is that the appropriateness and length of the stopping rule for cemiplimab is not clear-cut. The base case limit of 22 months is similar to the two year limit recommended in some NICE guidance for immunotherapies. However, NICE Committees have expressed concerns about the lack of evidence for optimum treatment duration and difficulty in stopping treatment in practice when patients appear to be experiencing benefit (References 37-39 in the ERG Report). Regarding cemiplimab, although the 22-month stopping rule reflects the maximum treatment duration in the phase II study protocol, this limit has not yet been reached, so does not inform the survival data currently used in the model, whereas these data have been influenced by the 12-month limit on treatment in the phase I study. - Regarding chemotherapy, in the company's base case all patients were assumed to complete 6 cycles of chemotherapy. The ERG believes this assumption to be unrealistic and consider that the scenario with a mean of 3 cycles of chemotherapy is more realistic.
Why this issue is important	- The model is sensitive to the assumed maximum duration of treatment
Questions for engagement	a. In clinical practice, how long would treatment with cemiplimab last? Up to 22 months, 24 months or until progression regardless of when that occurred? b. Would a stopping rule be appropriate or implemented in practice? c. Regarding chemotherapy how many cycles are patients likely to receive in clinical practice?

Technical team preliminary scientific judgement and rationale	- It is recognised that the company's base case assumptions on the duration of cemiplimab treatment are reasonable. However, a treatment cap of 24 months is preferred to reflect accepted stopping rules for immunotherapies in other recent NICE appraisals for example TA520 Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy and TA490 Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy - The ERG's preferred assumption is that patients would receive a maximum of 3 cycles of chemotherapy is considered more realistic
Summary of comments	- Comments received from clinical experts: • Anecdotal data from patients on dual immunotherapy who had to stop treatment because of immune-related toxicities suggests that there may be prolonged benefits even after stopping treatment. On this basis a treatment stopping rule seems reasonable but may be difficult to implement in practice because cemiplimab works as well as the early data suggest (in terms of efficacy and tolerability) patients will want to continue with it • Patients likely to receive 3 cycles of chemotherapy in clinical practice - Comments received from company (Sanofi): • The original 22 month stopping rule was chosen to reflect the design for the phase II cemiplimab trial, but Sanofi agree with the initial view of the NICE technical team that a stopping rule of 24 months is preferred given that this reflects accepted stopping rules in other recent NICE appraisals and have updated the base case accordingly. • Scenario analyses have also been performed to show the impact of adopting alternative stopping rules, see table 14 of company's technical engagement response appendix. • Sanofi also agree with the initial view of the NICE technical team that it is appropriate to assume 3 cycles of chemotherapy and have updated the base case accordingly - ERG considerations: • The changes implemented by the company are appropriate

<table>
<tr><td>Technical team scientific judgement after engagement</td><td>- There seems to be consensus that treatment duration assumptions initially preferred by the technical team are acceptable and relatively conservative but concern was expressed by some clinicians that implementing a stopping rule for patients who have not progressed would be difficult in practice so discussion of the following scenarios by the AC is required
<table>
<tr><th>Stopping rule used in cemiplimab arm[a]</th><th>Treat to progression (TTP) in all patients</th><th>TTP or up to a maximum of 24 months in non-progressed patients</th><th>TTP or up to a maximum of 22 months in non-progressed patients</th></tr>
<tr><td>ICER vs. chemotherapy (£/QALY gained)</td><td>62,332</td><td>45,693</td><td>43,979</td></tr>
<tr><td>ICER vs. BSC (£/QALY gained)</td><td>64,146</td><td>47,463</td><td>45,745</td></tr>
</table>
Bold text indicates company’s base case ICERs; treatment benefit was assumed to persist for 3 years in all scenarios; 3 chemotherapy cycles assumed in all scenarios</td></tr>
</table>

Issue 8 – Persistence of treatment benefits

Background/description of issue	- The long-term effects of cemiplimab are currently unknown. Median duration of response had not been reached in the clinical trials. The company’s follow-up data for cemiplimab are currently limited (median [redacted] months, to a maximum of 28 months). The company cite evidence of continued response to PD-1 inhibitors after treatment discontinuation. They also note that NICE committees have accepted that this persistence of effect is clinically plausible given the mechanism of response (e.g. 5 years for nivolumab in TA490). - In their base case analysis, the company set PFS and OS hazards equal to those for chemotherapy after 3 years – this effectively means that cemiplimab is assumed to have no further benefit after 3 years. The company argue this leads to conservative but clinically plausible long-term survival estimates. They also tested the impact of a good range of scenarios, from no further benefit after a maximum duration of treatment (22 months) to continued benefit throughout the 30-year time horizon. The model is sensitive to these changes.

Why this issue is important	- The model is sensitive to the assumed persistence of treatment benefit
Questions for engagement	a. Is it likely that the treatment effect of cemiplimab will wane over time? b. The company assumes that the benefit of cemiplimab will last 3 years – is this clinically plausible? If not how long would the benefit be expected to last? c. Could the next data cut provide information that could reduce uncertainty around persistence of treatment effects of cemiplimab?
Technical team preliminary scientific judgement and rationale	- The technical team note that a 5-year treatment benefit assumption has been accepted in prior NICE committees have accepted that this persistence of effect is clinically plausible (e.g. 5 years for nivolumab in TA490) - The technical team prefer the more conservative estimate of 3 years for treatment effects due to the uncertainty because the company's follow-up data for cemiplimab are currently limited.
Summary of comments	- Comments received from clinical experts: • 3 years is a reasonable estimate for a median response if treatment given for 22-24 months. However, this estimate may be too conservative. It could be longer especially if treatment given until disease progression. Data from the ongoing phase I and II studies have the potential to inform assumptions about duration of treatment benefit, including whether there is any waning of effect over time • Data from other immune checkpoint inhibitors suggest that a proportion of patients will show a very durable response, possibly for years - Comments received from company (Sanofi): • previous NICE appraisals have accepted that given the mechanism of action of this class of treatments a continued treatment benefit is clinically plausible and have accepted assumption for a persistence of the treatment effect up to 5 years • the impact of different assumptions has been tested in scenario analyses. - ERG considerations: • The changes implemented by the company are appropriate • The ERG agrees with the company that longer term follow up data from the phase II study would reduce the uncertainty around the persistence of the treatment effect

Technical team scientific judgement after engagement	- There seems to be consensus that the assumption initially preferred by the technical team (3-year treatment benefit after 24 months of therapy with no adjustment for waning effect) is acceptable but as this is not evidence-based, there is still considerable uncertainty - Feedback has confirmed this assumption is relatively conservative

Issue 9 – Adverse events costs and effect

Background/description of issue	- Disutility values assigned to the adverse events by the company were selected from previous NICE appraisals and QALY loss was calculated assuming a one-month duration of effects for all adverse events (CS Tables 27 and 28). Costs of treating adverse events were based on previous NICE appraisals, NHS Reference costs or PSSRU unit costs (CS Table 39). Adverse event costs and QALY loss were implemented as a one-off loss in the first model cycle. This omits the impact of lasting and late-onset adverse effects. • No loss of QALYs or costs were assigned for adverse events under BSC. • One-off loss of utility and costs applied in the first model cycle were cemiplimab ([redacted]) & chemotherapy ([redacted]) - The ERG considers that the cost and utility loss due to adverse events is likely to be underestimated in the company model, and is possibly biased in favour of cemiplimab (due to the omission of long-term and immune-related events) but acknowledge it is not clear whether the model is sensitive to assumptions about adverse event rates - Data Source for adverse Effects: The CS presents key adverse event data from the two pivotal studies (phase I, n=26; phase II n=137) and the integrated analysis set (n=163), described as the safety analysis set. Grade 3 or 4 adverse event rates for cemiplimab were estimated from the integrated analysis excluding patients who received a fixed dose of cemiplimab (n=140). The company explain that this was intended to align the sources of data for treatment effects and adverse events. However, it means that adverse event rates in the model differ from those estimated from the full safety analysis set (n=163), as reported in CS Table 13 and in section 3.3.6 in the ERG report. - The ERG considers that the full safety analysis set is a more appropriate source for estimating adverse event rates.
Why this issue is important	- Adverse event costs and QALY loss were implemented as a one-off loss in the first model cycle. This omits the impact of lasting and late-onset adverse effects.

Questions for engagement

a. Is the cost and utility loss due to adverse events likely to be underestimated in the company model or is the current approach acceptable because it has a small impact on the absolute cost and QALY losses?

Adverse event	AE rates (% of patients)		AE rates (% of patients)[a]	One off cost (£)
	Cemiplimab	Cemiplimab		
Skin infection	1.1%	NR	0.010	£143.20
Hypercalcaemia	2.1%	NR	0.007	£1,139.92
Failure to thrive	7.7%	NR	0.006	£3,179.70
Fatigue	1.8%	NR	0.006	£3,179.70
Hypokalaemia	1.8%	7.1%	0.007	£1,139.92
Stomatitis or oral mucositis	NR	8.6%	0.013	£998.38
Neutropenia	NR	32.6%	0.007	£325.49
Anaemia	0.9%	14.5%	0.006	£1,273.72
Thrombocytopenia	NR	7.7%	0.009	£325.49
Febrile neutropenia	NR	5.2%	0.008	£2,688.94

Source: CS Tables 25, 26, 28 and 39, and Clarification Response Table 19 and 19; [a] Assumes one month for duration of all events. NR not reported

b. Should the one-off approach to the disutility of adverse events be accepted given the minimal impact to the absolute cost and QALY loss?

c. In clinical practice, what are the potential late onset immune related adverse events that can be anticipated?

Technical team preliminary scientific judgement and rationale	- The absolute cost and QALY loss associated with adverse events in the company's model are small. - Other appraisal for PD-1 Inhibitors • In (TA366) Pembrolizumab for advanced melanoma not previously treated with ipilimumab, utility values were estimated using EuroQol EQ-5D data from KEYNOTE-006, by assuming that quality of life decreases as people approach the last months of life. The utility scores decreased from 0.82, for people who were more than 360 days before death, to 0.33 for people in the 30 days before death. • In (TA490) Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy. The impact of adverse events (AEs) on costs and utility was incorporated in the first cycle of the model (once only). Any all-cause Grade 3 or 4 AE were included if the incidence was ≥5% in either arm of the CheckMate 141 trial. The ERG for this appraisal considered the 'once only' approach not to be in line with best practice but did not regard this as a priority issue because the impact on the incremental outcomes was minimal. - The technical team prefer annual recurrence of adverse event cost and QALY loss for duration of treatment effects and equal adverse event QALY loss and costs for cemiplimab and chemotherapy. This is to account for late onset adverse events and in line with the model assumption on persistence of treatment effects, that is, cemiplimab PFS and OS hazards are set equal to chemotherapy hazards (assumed years of treatment effects) years from baseline

Summary of comments	- Comments received from clinical experts: • The costs and utility losses due to adverse events are not underestimated in the company's model. PD1 inhibitors are usually well tolerated • The impact of long-term adverse events is likely to be low in the population who are most likely to receive cemiplimab (even with effective treatment, because most people with CSCC are elderly, many patients will not live long enough for late-onset, chronic, irreversible adverse events to be considered a significant risk/burden) - Comments received from company (Sanofi): • The base-case has now been updated with the [redacted] data in the economic model while maintaining this original assumption (because these are considered acceptable by clinical experts). Results of this analysis can be found in Tables 12 and 13 of the company's technical engagement response appendix - ERG considerations: • The company do not directly address the question of whether the cost or utility loss due to adverse events (AEs) are underestimated in their model • despite reporting updated AE rates for cemiplimab based on the [redacted] safety dataset, the company have not revised the AE estimates in their model • The ERG still considers that the impact of AEs is likely to be underestimated in the company's revised cost-effectiveness estimates, as costs and effects of late onset AEs are omitted. However, this is not expect that this would significant impact on the ICER estimates, as absolute AE rates, and the associated costs and utility losses are small
Technical team scientific judgement after engagement	- There seems to be consensus that the company's original approach to modelling adverse events is acceptable (so the technical team accept the company's decision not to revise the assumptions in their updated analysis)

Issue 10 – Resource use in the pre-progression health state

Background/description of issue	- The company based estimates of resource use in the pre-progression health state on opinions from clinical experts with experience of treating this patient group in the NHS. The resulting assumptions about resource use for the pre- and post-progression health states are summarised in CS Tables 35 and 37. - Clinical experts consulted by the ERG noted that in some respects the company estimates of resource use seemed unrealistic for routine NHS practice. They suggested that before progression, the following would be more usual: • One consultation with an oncologist and blood tests very three weeks • Wound management nurse and dressings 4 times per month, but 10 for patients with locally-advanced disease (33/108) and 2 for metastatic disease (75/108). • Visits to both a tissue viability nurse and a clinical nurse every other month • Fewer palliative radiotherapy treatments (50% once every 3 months)
Why this issue is important	- Clinical experts consulted by the ERG noted that in some respects the company estimates of resource use seemed unrealistic for routine NHS practice
Questions for engagement	- Are the estimates of resource use in the pre-progression health state as expected in routine NHS practice?
Technical team preliminary scientific judgement and rationale	- The ERG's estimates for pre-progression resource use are more reflective of clinical practice.

Summary of comments	- Comments received from clinical experts: • the ERG estimates for pre-progression resource use are more likely to reflect NHS practice - Comments received from company (Sanofi): • Sanofi agree with the initial view of the NICE technical team that it is preferable to use the ERG's assumptions for pre-progression resource use and have updated in the economic accordingly (the base case results can be found in Tables 12 and 13 of the company's technical engagement response appendix) - ERG considerations: • The company have appropriately applied resource use estimates for the pre-progression health state along with updated unit costs in their updated base case analyses for the [redacted] data cut
Technical team scientific judgement after engagement	- There seems to be consensus that the ERG's estimates for pre-progression resource use are more reflective of clinical practice - The company's updates to the model are appropriate

Issue 11 – End of Life

<table>
<tr>
<td>Background/description of issue</td>
<td>
- The company's base case ICERs (including the CAA) are greater than the maximum usually considered a cost effective use of NHS resources. If the technology is deemed to be life-extending compared to current treatments, ICERs greater than what is usually considered a cost effective use of NHS resources can be considered, provided that all of the following criteria have been met:

  the treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
  there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.
  the estimates of the extension to life are sufficiently robust and
  the assumptions used in the reference case economic modelling are plausible, objective and robust.

- The company believe that consideration should be given to cemiplimab's life-extending potential and that the criteria above are met on the basis that:

  Median OS was reported at 15.1 months in a retrospective chart review of advanced CSCC patients receiving platinum-based chemotherapy. In the same study 100% of patients not receiving platinum chemotherapy had died by 12 months (median OS = 3.5 months; n=7)
  Modelled results for cemiplimab show a survival benefit of [redacted] months compared to current treatment (CS section B.2.13.2)

<table>
<tr><th>Technologies</th><th>Total life years</th><th>Incremental LYG</th></tr>
<tr><td>Chemotherapy/BSC</td><td>[redacted]</td><td>-</td></tr>
<tr><td>Cemiplimab</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained</td></tr>
</table>
- However, both the company and the ERG recognise that the modelled survival estimates are uncertain.
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</table>

Why this issue is important	- The company's base case ICERs (including the CAA) are greater than the maximum usually considered a cost-effective use of NHS resources. If the technology is deemed to meet the NICE criteria for special consideration, ICERs greater than what is usually considered a cost-effective use of NHS resources can be considered
Questions for engagement	a. What is the current life expectancy of the relevant patient population? b. How robust are the current estimates of survival benefit?
Technical team preliminary scientific judgement and rationale	- The NICE criteria are not met because the estimates of the extension to life are not sufficiently robust - The modelled overall survival in the comparator arm is greater than 2 years.
Summary of comments	- Comments received from clinical experts: • The current life expectancy of the relevant population is several months to 12 months maximum except in exceptional cases • the current estimates of survival benefit underestimate the comparative benefit afforded by cemiplimab because they overestimate the benefit from BSC or chemotherapy. - Comments received from company (Sanofi): • The company's comments reflected those of the clinical experts. • They also noted, that while the estimates are uncertain, cemiplimab is very likely to offer more than 3 months survival benefit when compared with the current standard of care because: • modelled survival estimates greatly exceed this showing a survival benefit of [redacted] months compared to current treatment • This was validated by the ERG demonstrating that even by using a set of pessimistic assumptions, cemiplimab was found to offer a gain of [redacted] life years ([redacted] months) compared to both chemotherapy and BSC (data in the above bullets are from the original company submission and ERG report) • when the latest available cemiplimab data based on the [redacted] is incorporated in the economic model the outcomes generated show consistent results compared to those when using the October 2017 data (survival benefit of [redacted] years)

	• a scenario analysis has now been conducted where survival of patients on chemotherapy is set at 1 year (see table 14 of the company's technical engagement response appendix) which demonstrates that the current base case is potentially conservative - ERG considerations: • The ERG's original "pessimistic" scenario analysis (ERG report section 5) estimated OS gain with cemiplimab at [redacted] months. The ERG report noted that median OS was not reached in the cemiplimab studies after a median of [redacted] months of follow-up and that the estimated 16-month OS rate was [redacted] From this the ERG concluded that cemiplimab likely offers a life-extending treatment for patients with a short life expectancy. The company's revised analysis with data from the latest cut ([redacted]) does not alter this conclusion but it needs to be emphasised that all the available survival estimates are subject to high uncertainty

<table>
<tr>
<td>Technical team scientific judgement after engagement</td>
<td>
- Uncertainties identified pre-engagement have not been fully resolved. Specifically, while there is consensus that life expectancy with current treatment is likely the be less than 2 years, as noted in Issue 6 above, the current survival estimates do not reflect this.
- It is unclear whether the estimates of the extension to life are sufficiently robust because:
• The company's updates to their economic analysis, while appropriate, have done little to resolve the uncertainty in the estimates of progression-free and overall survival that is due to:
▪ The reliance on an un-adjusted ITC (see issue 5)
▪ the small sample size, immaturity and uncertain generalisability (see issue 2) of the cemiplimab phase II trial data
• But there is also strong clinical consensus that the early trial results are promising and cemiplimab will be a beneficial treatment for patients with a high unmet need and extremely poor quality of life
• The technical team also recognise accept the points raised by the company and the ERG that there is a strong likelihood of >3 month survival benefit with cemiplimab
• The current undiscounted estimates of life years gained are as follows:
<table>
<tr><th>Technologies</th><th>Total life years</th><th>Incremental LYG</th></tr>
<tr><td>Chemotherapy/BSC</td><td>[redacted]</td><td>-</td></tr>
<tr><td>Cemiplimab</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">LYG, life years gained</td></tr>
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Issue 12 – Cancer Drug Fund

Background/description of issue	- If the appraisal committee concludes that estimates of the extension to life are not sufficiently robust, such that the uncertainty in the clinical and cost effectiveness data is too great to recommend the drug for routine use, the committee can consider a recommendation for use within the Cancer Drugs Fund (CDF) - In order for Cemiplimab to be eligible for the CDF there must be: • plausible potential for cemiplimab to cost-effective, • clinical uncertainty that, if resolved could allow the committee to recommended cemiplimab for routine commissioning, • the real potential for further data collection to address the identified clinical uncertainty - The company has stated that cemiplimab is a suitable candidate for the CDF and provided CAA base case ICERs. The company have also provided list price ICERs but have not provided any ICERs that include a patient access scheme (PAS) discount that would be relevant to routine commissioning - [redacted]
Why this issue is important	- If the technology is not recommended for routine use, the committee could recommend it for use in the CDF while additional data are collected that address the uncertainties in the evidence base.
Questions for engagement	a. Is the technology a good candidate for use in the CDF? Specifically, what additional value can the: • quarter 2 (2019) data cut of the phase II trial provide in terms of clarifying the uncertainty around overall survival estimates, the treatment stopping rule, the persistence of treatment benefits and the comparability of outcomes across dosing regimens. • Could data collection within the CDF resolve any of the uncertainty? b. What can Sanofi's ongoing retrospective chart review provide in terms of clarity around the comparative effectiveness of cemiplimab in the relevant population (Issues 3, 5 and 6)?
Technical team preliminary scientific judgement and rationale	- It is unclear whether additional data collection within the CDF could potentially reduce the uncertainty highlighted in this report. Given this the technical team request that the company make a case for routine commissioning, or explicitly describe how further data would reduce the key uncertainties.

<table>
<tr><td>Summary of comments</td><td>
- Comments received from clinical experts:

The [redacted] data cut:

will be too immature to give comparability of outcomes across dosing regimens.
will still be immature and median OS may not be reached if a tail (plateau in durable response) is demonstrated, however, this will reinforce the effectiveness of this treatment and show persistence of treatment benefits.

Cemiplimab is a good candidate for use in the CDF - data collection within the CDF should help resolve uncertainty around overall survival estimates, persistence of treatment benefits and comparability of outcomes across different dosing regimens
Inclusion of Cemiplimab on the CDF will enable us to get real world prospective data on the advanced CSCC which would be more robust than the retrospective data collection
For the patients not to be deprived of Cemiplimab, we would support the inclusion of Cemiplimab on the CDF

- Comments received from company (Sanofi):

Sanofi believe that cemiplimab is a potential candidate for use in the CDF given the level of uncertainty with the current evidence and the greater amount of certainty that the proposed data collection is anticipated to provide

Timelines by which the proposed data collection will become available
<table>
<tr><th>Proposed data collection</th><th>Date when the proposed data is expected to become available</th></tr>
<tr><td>Long term OS and PFS data from the phase II cemiplimab trial for all three cohorts of the Phase II trial:
Group 1: mCSCC on 3mg/kg q2w
Group 2: laCSCC on 3mg/kg q2w
Group 3: mCSCC on 350mg q3w</td><td>PFS and OS data from a [redacted] data cut (This could be fully incorporated into ITCs and the economic model by [redacted])</td></tr>
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</td></tr>
</table>

Data from the retrospective chart review study in the UK	Efficacy data will be available in [redacted] (with data fully incorporated in the economic model in [redacted])
Data from the retrospective chart review study in Europe and the US.	Efficacy data will be available in [redacted] (with data fully incorporated in the economic model in [redacted])
Collection of baseline characteristics and efficacy data through SACT for UK patients receiving cemiplimab.	[redacted] assuming a 2 year CDF data collection period.

How the proposed data collection will help address key areas of uncertainty

Area of uncertainty identified in the technical report	How proposed data collection if recommended for use on the CDF could reduce uncertainty
Clinical profile (including age) of patients who would receive cemiplimab in the UK	Collection of data through SACT will provide data from UK patients who are eligible and have received cemiplimab. This data will provide insights on the specific patients who are suitable for treatment with cemiplimab and their baseline characteristics.
Quality of the evidence for chemotherapy and best supportive care and the validity of the indirect treatment comparisons.	Collection of data through the retrospective chart review study will enable the creation of a UK-specific historical control arm of the current standard of care.
Plausibility of the extrapolated overall survival	Long term follow up data both on OS and PFS from the cemiplimab phase II trial will become available in [redacted]. This significantly longer term follow-up data can be used to increase the certainty around the long term survival predictions for cemiplimab. Supportive information on overall survival for cemiplimab could also be collected from the SACT database.

The maximum duration of treatment with cemiplimab (stopping rule) and the persistence of the cemiplimab treatment effect	Follow up data on the average treatment duration and the proportion of patients receiving treatment up to 22 months will be available from the planned data cut of the phase II trial in [redacted]. This data cut will also provide evidence on the continued treatment benefit beyond the 22-month treatment cap as applied in the phase II trial.
End of life and the extension of life	Long term follow up data on OS from the cemiplimab phase II trial data cut in [redacted] will increase the certainty around the long term survival data for cemiplimab.
Currently limited data is available from the phase II cemiplimab trial for patients receiving the fixed dose of 350 mg in line with the anticipated marketing authorisation	Follow up data from the cemiplimab phase II trial data cut in [redacted] will provide significant long term data from patients that received the fixed cemiplimab dose of 350 mg.

- ERG considerations:
  - the company have not directly answered NICE's question regarding how much of the uncertainty would be resolved by the [redacted] data cut of the phase II study in relation to uncertainty around OS estimates, the stopping rule, and persistence of benefits
  - Full data from the fixed-dose group of the phase II study, which reflects the dose regimen in the company's anticipated marketing authorisation, is not expected to be available until a data cut in [redacted]
  - The fixed-dose group only includes patients with metastatic CSCC patients and the company has not commented on whether any 350mg q3w fixed-dose data would be collected for patients with locally advanced CSCC
  - ERG comments on issue 5 regarding which uncertainties are likely/not likely to be resolved through the use of data from Sanofi's retrospective chart review are also relevant

Technical team scientific judgement after engagement	- Uncertainties identified pre-engagement have not been fully resolved. Specifically, while there is consensus amongst clinicians that entry into the CDF should be supported: • Data collection in the CDF is unlikely to resolve key uncertainties which arise from the lack of comparative studies for cemiplimab – any future estimates of relative effectiveness will still be based on an unanchored ITC that is likely to have significant limitations (see issue 5) • The timeframe for data collection in the CDF if not clear but meaningful data on the efficacy of cemiplimab are unlikely to be available until [redacted]

3. Issues for information

Table 2: List of Plausible ICERs and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	vs. chemotherapy	vs. BSC
		ICER	ICER
Updated company base case	**–**	**£45,693**	**£47,463**
A range of ICERs for patients aged 70-80 years should be considered	Patients who are eligible for treatment may vary in age	£45,693 to £55,931	£47,463 to £58,323
A range of ICERs reflecting different plausible timeframes for duration of treatment (issue 7) and persistence of treatment benefit (issue 8) should be considered	It is unclear whether a stopping rule can be implemented in practice or how long the benefits of cemiplimab would last	£43,979 to £62,332	£45,745 to £64,146

Table 3: Uncertainties in the evidence base that were not consulted on at technical engagement

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Small patient numbers	The clinical effectiveness evidence for cemiplimab comes from an integrated analysis of two ongoing single arm trials. N=149 patients were included in the integrated analysis in total; n=26 (17%) from the phase 1 trial and n=123 (80%) from the phase II trial (although as noted in issue 3b above the sample size of the integrated analysis population could be increased slightly if the n=44 patients who received the fixed-dose of cemiplimab were included). The relatively small sample size increases the risk that the study population is not representative of the population that will be seen in practice and limits the scope of population adjustment methods that can be used when performing ITC (see issue 5)	Unknown
Immature evidence base	At the most recent data cut, more than [redacted] of the patients that were included in the integrated analysis from the phase II trial were still alive. This means that survival estimates are based largely on extrapolation of very few observed events. The ERG considers that the current evidence base is too weak to draw reliable conclusions about cost-effectiveness.	Unknown

Table 4: Other issues for information

Issue	Comments
Full Incremental Analysis	The incremental analysis is not relevant if in practice the two comparators would not be considered as options for individual patients (for example, depending on fitness for chemotherapy).
Equality considerations	No equalities issues were identified.
Innovation	The company considered cemiplimab to be innovative noting that it offers a treatment option with a novel mechanism of action compared to currently used chemotherapy and BSC and was granted 'breakthrough designation' from the US Food and Drug Administration (FDA) due to the substantial improvement on a clinically significant endpoint over available therapies, but no evidence has been presented on benefits not captured in the measurement of the QALYs and the resulting cost-effectiveness estimates.

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