Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2216

cemiplimab 350mg concentrate for solution for infusion (Libtayo®)

Sanofi

10 January 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the end of life and orphan equivalent process

cemiplimab (Libtayo®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: As monotherapy for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or curative radiation.

In a phase II study of cemiplimab in patients with metastatic or locally advanced CSCC the objective response rate was 44%.

The base-case economic analysis submitted by the company assumed that patients were treated for a maximum of two years.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman, Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.[1]

Dosing Information

The recommended dose is 350mg cemiplimab, every 3 weeks, administered as an intravenous infusion over 30 minutes. Treatment may be continued until disease progression or unacceptable toxicity. No dose reductions are recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in the summary of product characteristics (SPC). Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.[1]

Product availability date

August 2019

Cemiplimab meets SMC end of life and orphan equivalent criteria for this indication.

It has conditional marketing authorisation from the European Medicines Agency (EMA).

Summary of evidence on comparative efficacy

Cemiplimab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody and is the first medicine to be licensed for this indication. It increases T cell responses including anti-tumour responses by binding to the programmed cell death-1 (PD-1) receptor and blocking its interaction with its ligands PD-L1 and PD-L2.[1, 2]

Key evidence for this indication is from EMPOWER-CSCC 1, an on-going, open-label, non-randomised, phase II study. The study recruited adults with a histologically confirmed diagnosis of invasive CSCC and at least one lesion that was measurable by study criteria (n=193). Recruited patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, and adequate hepatic, renal and bone marrow function. Patients with locally advanced CSCC were deemed to be inappropriate candidates for surgery or radiation therapy and had an investigator note which stated that the patient's advanced CSCC would likely be life-threatening within three years with currently available treatment outside of a clinical study.[2]

Patients were initially recruited to two groups, those with metastatic disease (group 1) and locally advanced disease (group 2). These patients received cemiplimab intravenously at a dose of 3mg/kg once every 2 weeks for up to 96 weeks. A further group, group 3, was later added and recruited patients with metastatic disease. Patients in group 3 received cemiplimab 350mg once every three weeks (the licensed dose) for up to 54 weeks or until unacceptable toxicity or confirmed disease progression occurred. The study protocol specified toxicity management and

the circumstances where dose interruption, reduction or discontinuation of study treatment were required.[2]

The primary outcome was objective response rate (ORR) according to independent central review in each group. The ORR was the proportion of patients with a best overall response of complete response or partial response, confirmed at time points at least four weeks apart.[2] ORR was determined using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or composite response criteria including RECIST 1.1 and assessment of digital medical photography for those with externally visible target lesions.[2] Results are presented in Table 1 below for ORR at the latest data cut-off (20 September 2018 for groups 1 and 3 and 10 October 2018 for group 2). At this point, the primary analysis was possible for the full study population as all patients had the opportunity for at least three response assessments. The median follow-up times were 16.5 months, 9.3 months and 8.1 months in groups 1, 2, and 3 respectively. Combined median follow-up was 9.4 months. Overall ORR was 44% and the lower limit of the confidence interval was considered to be clinically meaningful.[2]

The key secondary outcome was centrally reviewed duration of response. By the data cut-off, median duration of response had not been reached in any group. Median overall survival had also not been reached. Additional secondary outcomes are included in Table 1 below.[2]

Table 1: Primary outcome and selected secondary outcomes from EMPOWER-CSCC 1.[2]

	Group 1: Metastatic CSCC cemiplimab 3mg/kg once every 2 weeks (n=59)	**Group 2: Locally advanced CSCC cemiplimab 3mg/kg once every 2 weeks (n=78)**	**Group 3: Metastatic CSCC cemiplimab 350mg once every 3 weeks (n=56)**	**All patients (n=193)**
Objective response rate (95% CI)	49% (36% to 62%)	44% (32% to 55%)	39% (26% to 53%)	44% (37% to 51%)
Complete response	17%	13%	3.6%	11%
Partial response	32%	31%	36%	33%
Median KM estimation of PFS (ICR assessed)	18.4 months	NR	10.4 months	18.4 months
Number of PFS events	28	27	26	81
Duration of response >6 months	93% (27/29)	68% (23/34)	64% (14/22)	-

CSCC: cutaneous squamous cell carcinoma, CI: confidence interval, ICR: independent central review, KM: Kaplan-Meier, NR: not reached, PFS: progression-free survival.

Patient reported quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). In general, changes in mean EORTC QLQ-C30 scores did not indicate consistent changes in quality of life apart from the pain symptom subscale which indicated improvement. No negative effects were observed in any of the subscales.[2]

In the absence of direct evidence comparing cemiplimab with platinum-based chemotherapy and best supportive care (BSC), the submitting company presented a naïve (unadjusted) indirect comparison and the results were used in the base case economic analysis. The outcomes reported for this analysis were overall survival, progression free survival (PFS), and ORR against platinum-based chemotherapy and overall survival against BSC. All analyses were unanchored and the three studies included were all single arm. Data were included from EMPOWER-CSCC 1 study for cemiplimab and two retrospective cohort studies for the comparators.[2-4] A simulated treatment comparison (STC), and match adjusted indirect comparison (MAIC) were conducted as sensitivity analyses and the results used in the economic analysis.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The EMA concluded that no new unexpected safety concerns had been identified for cemiplimab and that, taking into account the disease and patient population being treated, the safety profile is as would be expected from an anti-PD-1 antibody. Further safety data are to be gathered from the EMPOWER-CSCC 1 study as part of the specific obligations for the EMA conditional marketing authorisation.

Safety data are available from 591 patients treated with cemiplimab, of these 219 have advanced CSCC. Almost all patients (99%) had a treatment-emergent adverse event (TEAE). Serious TEAEs were reported in 31% of patients and TEAEs leading to treatment discontinuation were reported in 6.9% of patients. Immune-related adverse reactions occurred in 20% of patients and led to permanent discontinuation of cemiplimab in 4.4% of patients. The most common immune-related adverse events were hypothyroidism (7.1%), pneumonitis (3.7%), immune-related skin adverse events (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%). Other commonly reported TEAEs included diarrhoea, stomatitis, rash, pruritus, musculoskeletal disorders, and fatigue. Infusion-related reactions occurred in 9.1% of patients including 1 patient with a Grade 3 infusion-related reaction.[2] Of the 591 patients in total treated with cemiplimab, 12 patients (2%) had a fatal TEAE.[2]

None of the patients included in the immunogenicity population in EMPOWER-CSCC 1 (n=140) developed anti-drug antibodies (ADAs) or neutralising antibodies to cemiplimab. Concerns were noted by the EMA regarding the sensitivity of the ADA test and data were too limited to make any conclusions. This has been included in the risk management plan.[2]

The SPC notes that severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with cemiplimab treatment.[1]
No comparative safety data are available. Refer to the SPC for details.

*Other data were also assessed but remain confidential.**

Summary of clinical effectiveness issues

Ultraviolet (UV) light exposure is a key risk factor for CSCC. Other factors that add to this include sun damaged skin, skin that burns easily/doesn't tan, light-coloured hair, northern European descent, older age, exposure to PUVA phototherapy, immunosuppression (for example immunosuppressive medication after organ transplantation or for inflammatory disease, and those with lymphoma or leukaemia), exposure to radiation and other industrial carcinogens, and smoking. Male sex, and chronic inflammation are also associated with an increased risk of CSCC. The incidence of CSCC is rising in many countries.[2, 6]

Most patients with CSCC are initially treated with local treatment such as surgical excision, cryotherapy, electrosurgery, and radiation therapy, with cure being the aim of treatment. Recurrence rates are low and most local recurrences can be surgically removed. Metastatic CSCC or locally advanced CSCC, develops in a small percentage of patients, estimated to be less than 5%.[2, 6] Prognosis is very poor in these patients and median overall survival has previously been reported as 10.9 months and 3-year overall survival rate as 22%.[3]

There are no other licensed treatments available for advanced CSCC.[2] Patients may be treated with chemotherapy if they are fit enough, for example with platinum based regimes, such as cisplatin and fluorouracil. Clinical experts note that chemotherapy may not be suitable for many patients with advanced CSCC due to age, fitness, other co-morbidities and the toxicity of chemotherapy. Consequently, many patients with advanced CSCC will receive palliative care. Clinical experts consulted by SMC considered that cemiplimab fills an unmet need as there is currently no standard effective treatment for patients with advanced CSCC. Cemiplimab meets SMC end of life and orphan equivalent criteria for this indication.

The introduction of cemiplimab would provide a licensed treatment option for patients with metastatic or locally advanced CSCC. Clinical experts consulted by SMC considered that cemiplimab is a therapeutic advancement due to the ORR demonstrated in clinical studies. They considered that the place in therapy is first-line treatment for patients with advanced CSCC not suitable for curative surgery or radiotherapy.

Key strengths

- The phase II study EMPOWER-CSCC 1 in patients with metastatic or locally advanced CSCC treated with cemiplimab reported an ORR of 44% and the lower limit of the confidence interval was considered to be clinically meaningful. ORR is not a direct health outcome but it was considered by the EMA to be clinically relevant particularly when considering ORRs for other treatments.[2]
- The EMA also noted that the duration of response of >6 months in 93% of patients in group 1 further supports the efficacy of cemiplimab, although data are not yet mature for the full study population.[2]

Key uncertainties

- This was a single arm study, and so no direct comparative data are available. The indirect comparison presented by the company was naïve and associated with substantial limitations including: the use of retrospective data, subject to potential bias and confounding; heterogeneity across the studies; wide variation in duration of follow up; no common comparator arms; and small sample size. Overall, due to these limitations, no firm conclusions can be drawn from the indirect treatment comparisons.
- There was a limited duration of follow-up in EMPOWER-CSCC 1 (9.4 months overall) and additional outcomes, for example duration of response, overall survival and long-term safety, are awaited. In addition, the magnitude of the effect of cemiplimab is not yet clearly defined.[2] Only patients in group 3 received cemiplimab at the licensed dose (n=56). This group included metastatic patients and not those with locally advanced disease. There is uncertainty in the safety of cemiplimab at the licensed dose due to the small patient numbers and short duration of follow-up at present.[2]
- Patients with a history of solid organ transplant and those with significant autoimmune disease were excluded from the key study.[2] Immunosuppression is a risk factor for CSCC therefore some of the relevant patient population are not likely to be suitable for treatment with cemiplimab.

Cemiplimab has an EMA conditional marketing authorisation. To confirm the efficacy and safety of cemiplimab in this patient population, the marketing authorisation holder is required to submit the final study report for the key phase II study by 31 October 2022. They are also required to conduct a prospective single-arm study in the same population at the licensed dose of 350mg once every three weeks and provide interim data by 31 March 2023. They are required to investigate biomarkers in order to confirm that PD-L1 expression is not predictive of efficacy. Assessment of other potential biomarkers that may affect efficacy is recommended.[2]

SMC considered that the EMA specific obligations may address some of the key uncertainties in the clinical evidence presented.

*Other data were also assessed but remain confidential.**

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of cemiplimab, as an orphan-equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metastatic or locally advanced CSCC not suitable for curative surgery or radiation, is a severe, life-limiting condition. It has a significant impact on quality of life for patients and their carers and families. Tumours affect the exposed head and neck area and are unsightly, painful, foul smelling, and may bleed or weep. This can be very upsetting for patients causing them to be self-conscious about their appearance leading to social isolation.
- No effective standard treatments are available and there is significant unmet need. Chemotherapy is a potential treatment option but evidence of efficacy is very limited and it is associated with significant toxicity. Patients are often older and unsuitable for chemotherapy which means can only receive palliative therapies, such as radiotherapy, for symptom control. The radiotherapy mask is immobilising which can be traumatic particularly for older, frail patients.
- PACE participants noted that the response rates demonstrated in clinical studies suggest that cemiplimab may address the unmet need for this patient population. It could be offered as first line treatment in both young fit patients and elderly patients.
- Symptom control and improving quality of life are key outcomes for patients. A positive tumour response with cemiplimab treatment could improve symptoms such as pain and reduce the unsightly nature of the condition therefore improving quality of life. There would also be a positive psychological benefits of having a treatment option. The burden of care would be expected to reduce, for example less weeping tumours would mean less laundry.
- Cemiplimab is given as a short intravenous infusion every 3 weeks on an outpatient basis and does not require frequent or lengthy hospital visits. It is likely to be a tolerable treatment with adverse events similar to other immune checkpoint inhibitors.

Additional Patient and Carer Involvement

We received a patient group submission from Melanoma Action and Support Scotland (MASScot), which is a Scottish Charitable Incorporated Organisation (SCIO). MASScot has received 2.3% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from MASScot participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis (CUA) comparing cemiplimab to platinum-based chemotherapy (cisplatin plus fluorouracil) and to best supportive care (BSC) for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or curative radiation. SMC clinical expert feedback agrees that platinum-based chemotherapy and BSC are both relevant comparators.

The economic analysis used a partitioned survival model with three health states (pre-progression, post-progression and death). The model adopted a lifetime horizon of 30 years.

The clinical data for cemiplimab were taken from the single-arm phase II EMPOWER-CSCC 1 study, which informed the patient baseline characteristics (age, weight, gender), PFS and overall survival for cemiplimab, treatment duration including stopping rules for cemiplimab, health-related quality of life (HRQoL), and adverse events for the economic model. A single-arm study[3] consisting of a mixed cohort of advanced CSCC patients was used to determine PFS and overall survival estimates for chemotherapy. These data were used as a proxy for BSC due to limitations in PFS/OS data identified for BSC. As no comparative data were available from the cemiplimab key study, indirect treatment comparisons (ITCs) were conducted to enable a comparison with chemotherapy and BSC. To inform the comparative effectiveness of cemiplimab the naïve (unadjusted) comparison described above was used in the base case with the use of the STC and MAIC explored in scenario analysis.

PFS and overall survival were modelled independently for cemiplimab and platinum-based chemotherapy with alternative parametric models fitted to the observed data for each of the interventions, with the best fitting curve chosen based on goodness of fit statistics and clinical plausibility. For overall survival and PFS, the lognormal function was selected for estimation of long-term cemiplimab outcomes.

A 24-month stopping rule was included in the economic analysis for all patients who had not previously discontinued or died, and a continuation of treatment benefit for cemiplimab was assumed to be maintained for three years following discontinuation. Treatment duration for chemotherapy was assumed to be three cycles.

Utility values, which were age adjusted, for the pre-progression and post-progression health states were derived from mapping EORTC QLQ-30 data collected within the phase II EMPOWER-CSCC 1 study to the EQ-5D-3L based on a published algorithm.[7] Disutilities for selected treatment specific adverse events were also included, with decrements sourced from published studies.

Costs included medicine acquisition, medicine administration, health state monitoring, treatment of adverse events, and terminal care. Resource use for routine follow-up care were estimated based on a survey of UK clinical experts.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

In the base case for cemiplimab versus platinum-based chemotherapy the incremental cost-effectiveness ratio (ICER) is estimated at £41,637 per quality adjusted life year (QALY) with the PAS applied (Table 2), and versus BSC was estimated at £43,691/QALY with PAS (Table 3). The main driver of increased costs was additional medicine acquisition costs for cemiplimab compared to chemotherapy and BSC, as well as increased monitoring costs for post-progression patients.

Table 2: Base case results cemiplimab versus chemotherapy at PAS prices

Treatment	ICER (cost/QALY)
cemiplimab	£41,637

Table 3: Base case results cemiplimab versus best supportive care (BSC) at PAS prices

Treatment	ICER (cost/QALY)
cemiplimab	£43,691

ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year

In one way sensitivity analysis the ICER was most sensitive to variation in the parameters used for estimation of OS and PFS, post-progression costs and utilities. A range of scenario analyses were performed which resulted in a range of ICERs between £29,933-£56,237/QALY at PAS price with the scenarios most sensitive on the ICER being alternative utilities, long-term extrapolations and a shorter treatment benefit duration (Table 4).

Table 4: Selected scenario analysis results (cemiplimab vs platinum-based chemotherapy and vs BSC) at PAS price

	Scenario	ICER versus chemotherapy (PAS price)	ICER versus BSC (PAS price)
Base case		£41,637	£43,691
1	Comparative efficacy: using a Simulated Treatment Comparison (STC)	£35,352	£36,825
2	No additional cemiplimab benefit after 2 years stopping rule applied (instead of an additional 3-year continued treatment benefit in the base case)	£50,060	£52,834
3	No additional treatment benefit after 5 years (instead of an additional 3-year continued treatment benefit in the base case)	£36,296	£37,919
4	Alternative OS curve fits for cemiplimab: Weibull	£43,140	£45,333
5	Alternative OS curve fits for chemotherapy: Lognormal	£50,638	£53,537
6	OS for chemotherapy and BSC based on the upper confidence interval [OS HR = 0.58 for chemotherapy, OS HR = 0.33 for BSC] from the naïve indirect treatment comparison, base case PFS	£50,272	£53,125

7	Utilities: EQ-5D mapped from Phase II EORTC-QLQ30 - SCCHN utilities in NICE TA473 (utilities of 0.67 and 0.52 for pre and post progression states respectively)	£56,237	£59,069
8	Time horizon: 10 years	£48,465	£51,229
9	Long term extrapolations of cemiplimab, chemotherapy and BSC: based on a clinical expert elicitation exercise	£29,933	£30,371

SCCHN: squamous cell carcinoma of the head and neck

In addition to the high base case ICERs, there were a number of weaknesses and uncertainties in the economic analysis:

- The main clinical evidence for cemiplimab is based on a single-arm, phase II study with small patient numbers. PFS and overall survival data are currently immature. As a consequence the estimates of duration of treatment effect and overall survival are uncertain and as shown, the results are sensitive to the use of alternative assumptions or methods used to derive their estimation. Clinical evidence for chemotherapy and BSC are also limited and are based on a subset of 18 patients who received platinum-based chemotherapy in a non-UK retrospective chart review.[3]. There are also generalisability issues of the studies to a Scottish population.
- The lack of comparative evidence for cemiplimab versus platinum-based chemotherapy and BSC meant an ITC was necessary, with a naïve comparison used in the base case, and BSC assumed to have the same efficacy as chemotherapy. This had limitations as expressed in the summary of clinical effectiveness issues section above. Due to these limitations, the PFS and overall survival hazard ratios and estimates of relative effectiveness lack robustness and are highly uncertain. Setting the PFS hazard ratio at one did not have a major impact on the ICERs but various scenario analyses presented in the submission or requested from the company indicate that variation in relative OS estimates are impactful on the ICERs. Applying the results of the simulated treatment comparison conducted as an alternative ITC resulted in lower ICERs of £35,352/QALY and £36,825/QALY versus chemotherapy and BSC respectively (with similar results associated with the MAIC), but based on the relative clinical data available these results lack robustness. A scenario analysis in which modelled PFS and OS estimates for cemiplimab and comparators were adjusted through an clinical expert survey and consensus meeting exercise resulted in lowest estimated ICERs (scenario 9, Table 4), whereas a scenario analysis using the upper confidence of the ITC for the comparators led to ICER estimates of £50,272/QALY and £53,125/QALY versus chemotherapy and BSC (scenario 6, Table 4).
- The utility estimates used in the base case for the pre and post progression health states appear high. Applying alternative utilities from a squamous cell cancer of the head and neck NICE appraisal (of 0.67 and 0.52 for pre and post progression)[8] resulted in an increased ICER of £56,237/QALY versus chemotherapy and £59,069 versus BSC, with PAS (Table 4, scenario 7).
- Time on treatment for cemiplimab is set to 24 months with the duration of treatment benefit assumed as three years following treatment discontinuation. It is unclear on what evidence this is based, so is uncertain. Assuming no additional benefit after treatment discontinuation increased the ICER (table 4, scenario 2).

The Committee also considered the benefits of cemiplimab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as cemiplimab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted cemiplimab for use subject to ongoing evaluation and reassessment in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published Management of primary cutaneous squamous cell carcinoma; A national clinical guideline (SIGN 140) in June 2014.[6] This guideline make recommendations on a number of treatment options for primary CSCC but limited recommendations are made regarding the treatment of advanced disease.[6, 9] The guidance does recommend that consideration is given to the use of chemotherapy in patients with metastatic CSCC.[6]

The British Association of Dermatologists (BAD) originally published multi-professional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma in 2002.[9] The guidance was subsequently updated in 2009 and is currently being reviewed.

The European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC) published Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline in 2015.[10] This guidance is broadly in concert with the SIGN guidance but recommends that: Mono- or poly-chemotherapy can be used in metastatic CSCC; however, there is no established standard regimen and responses are usually short-lived.[10]

Additional information: comparators

No standard therapy. Best supportive care or chemotherapy (potentially with cisplatin and fluorouracil).

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
cemiplimab	**350mg IV once every 3 weeks**	**80,600**

IV: intravenous. Costs from eMC Dictionary of Medicines and Devices Browser on 23 August 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 49 patients eligible for treatment with cemiplimab in year 1 and year 2, rising to 50 patients in years 3, 4 and 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. Sanofi. Cemiplimab concentrate for solution for infusion (Libtayo®). Summary of product characteristics. European Medicines Agency www.ema.europa.eu. Last updated: 03/07/19.
2. The European Medicines Agency (EMA) European Public Assessment Report. Cemiplimab (Libtayo®). 26/04/2019, EMEA/H/C/004844/0000 www.ema.europa.eu.
3. Jarkowski A, Hare R, Loud P, Skitzki JJ, Kane JM, May KS*, et al.* Systemic Therapy in Advanced Cutaneous Squamous Cell Carcinoma (CSCC): The Roswell Park Experience and a Review of the Literature. American journal of clinical oncology. 2016;39(6):545-8. Epub 2014/06/01.
4. Sun L, Chin R, Gastman B, et al. Association of Disease Recurrence With Survival Outcomes in Patients With Cutaneous Squamous Cell Carcinoma of the Head and Neck Treated With Multimodality Therapy. JAMA Dermatol. 2019;155(4):442-7.
5. *Commercial in Confidence**
6. Scottish Intercollegiate Guidelines Network. Management of primary cutaneous squamous cell carcinoma; A national clinical guideline (SIGN 140). 2014. Avaialble at: https://www.sign.ac.uk/sign-140-management-of-primary-cutaneous-squamous-cell-carcinoma.html (Accessed: 09/08/19)
7. Longworth L, Rowen D. Mapping to Obtain EQ-5D Utility Values for Use in NICE Health Technology Assessments. Value in Health. 2013;16(1):202-10.
8. National Institute for Health Care Excellence. TA473: Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck. 2017 31 August 2017 [cited; Available from: www.nice.org.uk.
9. Motley R, Preston PW, Lawrence C, British Association of Dermatologists. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. 2009. Available at: http://www.bad.org.uk/library-media%5Cdocuments%5CSCC_2009.pdf (Accessed: 09/08/19).
10. Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H*, et al.* Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. European journal of cancer (Oxford, England : 1990). 2015;51(14):1989-2007. Epub 2015/07/30.

This assessment is based on data submitted by the applicant company up to and including 11 October 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.