NICE National Institute for Health and Care Excellence

NICE guidance

Cemiplimab for treating advanced cutaneous squamous cell carcinoma

Technology appraisal guidance
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www.nice.org.uk/guidance/ta802

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance replaces TA592.

1 Recommendations

1.1 Cemiplimab is recommended as an option for treating metastatic or locally advanced cutaneous squamous cell carcinoma in adults when curative surgery or curative radiotherapy is not suitable, only if:

- it is stopped at 24 months, or earlier if their disease progresses, and
- the company provides cemiplimab according to the commercial arrangement.

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund for cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma (NICE technology appraisal guidance TA592).

Standard care for people with advanced cutaneous squamous cell carcinoma is best supportive care so there is a need for effective and well-tolerated treatment options.

The new clinical evidence includes additional data from a clinical trial and from people having cemiplimab in the NHS while it was available in the Cancer Drugs Fund. People in the clinical trial and Cancer Drugs Fund followed a stopping rule which meant they stopped treatment at 22 months and 24 months respectively, or earlier if their disease progressed. There are no trials directly comparing cemiplimab with best supportive care. But an indirect comparison suggests that people taking cemiplimab are likely to live longer than people having best supportive care. There is still not enough data from the Cancer Drugs Fund and the trial to be certain by how much cemiplimab increases the length of time people live.

Because of the uncertainty with the clinical data, the cost-effectiveness estimates are also uncertain. The life expectancy of people with advanced cutaneous squamous cell carcinoma receiving best supportive care, and the evidence for how long life might be extended with cemiplimab, meet the end of life criteria. Therefore, the most likely cost-effectiveness estimates fall within what NICE considers an acceptable use of NHS resources. So, cemiplimab is recommended for routine use.

2 Information about cemiplimab

Conditional marketing authorisation indication

2.1 Cemiplimab (Libtayo, Sanofi) 'as monotherapy is indicated 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cemiplimab.

Price

2.3 The list price for cemiplimab is £4,650 per 350 mg vial (excluding VAT; BNF online accessed April 2022). The cost per course of treatment is £4,650. The cost for 1 year of treatment with cemiplimab based on the list price is £80,877.

2.4 The company has a commercial arrangement. This makes cemiplimab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by the company, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

This review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal. Further information about the original appraisal is in the committee papers. Data was collected on the use of cemiplimab in the NHS through the Cancer Drugs Fund using the Systemic Anti-Cancer Therapy (SACT) dataset. As a condition of the Cancer Drugs Fund's managed access agreement, the company was required to collect updated efficacy data from the EMPOWER-CSCC 1 study for people with metastatic or locally advanced cutaneous squamous cell carcinoma. The company also collected data on the effectiveness of treatment with platinum-based chemotherapy and with best supportive care in the UK through a retrospective chart review.

Clinical need and current management

Living with advanced unresectable cutaneous squamous cell carcinoma is physically and emotionally challenging

3.1 Cutaneous squamous cell carcinoma (CSCC) is a distinct disease that differs from malignant melanoma and other squamous cell carcinomas such as primary head and neck or lung squamous cell carcinoma. Risk factors include exposure to ultraviolet radiation, increasing age, and immunosuppression. Early CSCC can be cured in most people, but in a small proportion of people the disease reaches an advanced state (metastatic or locally advanced) that cannot be removed with surgery (unresectable) or cured with radiotherapy. Often, people with advanced disease are older, have other comorbidities, and have a poor prognosis. The skin lesions can grow to be quite large and the disease can spread to different parts of the body. Because of the link with ultraviolet exposure, the lesions often develop on parts of the body that are visible, such as the face. The patient expert described how advanced CSCC can be extremely debilitating because it can result in unpleasant foul-

smelling wounds. Living with advanced unresectable CSCC is challenging and, because of the visibility of the disease, it often results in people avoiding social interaction. Caring for a person with CSCC can be physically and emotionally draining. The committee concluded that living with advanced unresectable CSCC is physically and emotionally challenging for both people with the disease and their carers.

Best supportive care is the most appropriate comparator

3.2 The company presented clinical and cost-effectiveness evidence for cemiplimab compared with platinum-based chemotherapy and best supportive care. The clinical experts stated that very few people aged over 70 would be offered platinum-based chemotherapy in the NHS, because of its side effects and lack of clinical benefit. People with advanced CSCC are typically older, and therefore are less likely to be able to tolerate platinum-based chemotherapy. The committee heard from the NHS England expert that in the SACT dataset 75% of people were aged 70 and above and 36% were aged 80 and above. The clinical experts stated that in their experience, the number of people who receive chemotherapy is less than 5%, and probably less than 2%. The patient expert stated that there are limited treatment options for this patient group, very few patients are offered radiotherapy and this rarely works. Therefore, treatment for most people with advanced unresectable CSCC is limited to best supportive care. The committee agreed that platinum-based chemotherapy is not routinely used for treating advanced unresectable CSCC in the NHS and therefore concluded that best supportive care is the most appropriate comparator for this appraisal.

Cemiplimab is a highly valued and well tolerated treatment option for people with advanced unresectable CSCC

3.3 The clinical and patient experts described the substantial burden of advanced unresectable CSCC on quality of life and the lack of current treatment options. One clinical expert emphasised that because local disease can result in large, fungating tumours, it is particularly important to also consider progression-free survival when assessing the benefits of cemiplimab. The committee also heard that people who respond to

cemiplimab can experience substantial benefits, that tumours shrink, and some people remain disease free for 2 years. In addition, the committee heard that single agent immunotherapies are generally well tolerated, including in older people. One of the clinical experts stated that the most common side effects of cemiplimab are fatigue and rashes, which can be easily resolved. Some people can experience more serious autoimmune side effects. These are generally manageable and can be resolved with high-dose steroids or by having a treatment break. The committee noted cemiplimab's benefits for those who respond and concluded that cemiplimab is a highly valued treatment option for people with advanced unresectable CSCC.

Clinical evidence

Trial data for cemiplimab is promising but it has not been directly compared with other treatments

3.4 Data on response and survival outcomes for cemiplimab was reported in 2 single-arm trials: a phase 1 trial and an ongoing phase 2 trial known as EMPOWER-CSCC 1. The phase 1 trial included 26 people with metastatic and locally advanced CSCC who had a cemiplimab dose of 3 mg per kg every 2 weeks for up to 48 weeks. In EMPOWER-CSCC 1, two groups of people had a cemiplimab dose of 3 mg per kg every 2 weeks with a stopping rule which stopped treatment at 96 weeks (22 months), or sooner if disease progressed. One of the groups had metastatic CSCC (59 people) and the other had locally advanced CSCC (78 people). A third group of 56 people with metastatic CSCC had the licensed cemiplimab dose of 350 mg every 3 weeks, with a stopping rule of up to 54 weeks, or sooner if disease progressed. The results were consistent between groups and the company presented this data pooled together in a base-case integrated analysis population. Across the 219 people included in the pooled company trials, 40% had locally advanced disease and 60% had metastatic disease. The median age was 72 years and 83% of people were male. All the people in the company trials had an Eastern Cooperative Group (ECOG) performance status of 0 (44% of people) or 1 (56% of people). At the October 2019 data cut-off for EMPOWER-CSCC 1, the objective response rate was 46.1% (95% confidence interval

38.9% to 53.4%) and median overall survival had not been reached after a median follow up of 15.7 months. The company submitted the results from the most recent data cut in July 2021, however these are academic in confidence and cannot be presented in full here. Median overall survival had not been reached at the July 2021 data cut-off. The committee concluded that the trial data for cemiplimab is promising because of the response rate seen in the trial population, but it has not been compared with other treatments, and the long-term overall survival benefit is uncertain.

There are differences between the cemiplimab trial data and SACT dataset, so there is uncertainty about whether the cemiplimab trial results are generalisable to UK clinical practice

3.5 Through the Cancer Drugs Fund, SACT data was collected from people having a cemiplimab dose of 350 mg every 3 weeks for metastatic or locally advanced CSCC in UK clinical practice. Between 2 July 2019 and 1 March 2021, 352 people had cemiplimab with a stopping rule of up to 24 months, or sooner if disease progressed, with a median follow up of 10.2 months. People in the SACT dataset had a median age of 77 years, 81% had an ECOG performance status score of 0 or 1, and 49% of people had locally advanced disease. Median overall survival in the SACT population was 21 months. The ERG noted that people in the SACT dataset were older than in the company trials and that overall survival was lower. Therefore the ERG expressed concerns about the generalisability of the company trials to UK clinical practice. The company stated that the SACT data shows that older and sicker patients could be treated with cemiplimab. The company also highlighted that there are limitations with the SACT dataset, including the unknown impact of the COVID-19 pandemic, limited information on patient characteristics and the shorter follow up compared with the company trials. The company stated that this makes it difficult to determine the generalisability of the company trials to UK practice using the SACT dataset. The clinical experts explained that clinical trials typically include a more selected population in terms of age and fitness, therefore results are expected to be more favourable than in clinical practice. In addition, it is likely that the COVID-19 pandemic impacted treatment with cemiplimab in the SACT dataset, for example, through missed doses,

people presenting later in the disease course and mortality because of COVID-19. However, the extent of the impact of the COVID-19 pandemic is unknown, resulting in additional uncertainty. The clinical experts also stated that the SACT dataset is immature and included people treated by clinicians with little or no experience of using cemiplimab. The clinical experts expected that clinical outcomes with cemiplimab would improve as clinicians become more experienced and learn who should be treated with cemiplimab and when to start treatment. The committee discussed whether the lower overall survival in the SACT dataset than in the trial population may be because of the reduced life expectancy of the older population in the SACT dataset. It discussed the possibility of more deaths from non-cancer causes, but noted that this was uncertain because the SACT data does not include cause of death, and neither the SACT data nor the company clinical trials included comparator arms. The committee agreed that there were differences in the patient characteristics and the outcomes between the clinical trials and the SACT dataset and concluded that it was uncertain whether the cemiplimab clinical trial results are generalisable to UK clinical practice.

The overall survival estimates with best supportive care are very uncertain

3.6 Comparator data in advanced CSCC is extremely limited. Because chemotherapy is not considered to be a relevant comparator for this appraisal (see section 3.2), only the evidence for best supportive care is discussed here. The company conducted a retrospective chart review to address the lack of comparative evidence that was highlighted during the original appraisal. The chart review was done between 1 January 2011 and 31 December 2015 and included 106 people with metastatic or locally advanced CSCC in the UK. However, both the company and the ERG agreed that the chart review lacks face validity, because of concerns about the comparability of the chart review population and the EMPOWER-CSCC 1 population. Also, the population characteristics and results were highly uncertain. In addition, very few people included in the chart review had CSCC that was eligible for best supportive care. Therefore, the analysis was limited to people receiving chemotherapy, which was not considered to be a relevant comparator by the committee. In the company's base-case analysis, the estimates for

the clinical effectiveness of best supportive care were based on evidence from a non-UK retrospective chart review (Sun et al. 2019). Data was used from a subset of 20 non-immunocompromised people with unresectable head and neck CSCC. Patient characteristics were not reported for this specific subset, however patient characteristics of the wider study population were generally similar to the cemiplimab trials. The median overall survival in the subset of non-immunocompromised people receiving best supportive care was 5 months. A committee member suggested that these reviews may reflect clinical practice better than a clinical trial. However, the company explained that the estimates of survival for best supportive care from the Sun et al. chart review are likely to be more favourable than in clinical practice. This is because the Sun et al. study included a highly selected population who were treated in academic treatment centres. The ERG agreed that the study population was highly selected and noted that the results are very uncertain because of the small study population. The clinical expert explained that there is a lack of survival data for people with advanced CSCC, partly because the lack of treatment options means that people are usually discharged back to primary care and are not followed up in the hospital setting. The committee concluded that the estimates of survival with best supportive care are very uncertain.

Indirect comparisons

None of the indirect comparisons provide a reliable estimate of cemiplimab's effectiveness

3.7 There are no available studies directly comparing cemiplimab with best supportive care, so the company did an indirect treatment comparison (ITC). For the comparison of cemiplimab with best supportive care the company explored 2 ITC methods: a simulated treatment comparison (STC) and a matching-adjusted indirect comparison (MAIC). The company also presented the results of a naive comparison, which fitted survival extrapolations directly to the observed data. The results from all 3 methods suggest that people who had cemiplimab had a longer overall survival than people who had best supportive care. The ERG noted that the company's approach to the ITC was systematic and in line with the

recommendations in the technical support document published by the Decision Support Unit. The committee noted that the ITC is based on comparator data that is considered highly uncertain and concluded that none of the indirect comparisons provide a reliable estimate of relative effectiveness. However, the committee agreed that it was likely that cemiplimab extended survival compared with best supportive care.

The company's economic model

The company model is suitable for decision-making

3.8 As in the original appraisal, the company modelled cost effectiveness using a partitioned survival model with 3 health states (pre-progression, post-progression and death). The model had a 30-year time horizon and a monthly cycle length with a half-cycle correction. A 2-year stopping rule was applied for cemiplimab which is similar to the 22-month stopping rule applied for 2 of the groups in the EMPOWER-CSCC 1 study (see section 3.4) and was agreed in TA592. The company extended the assumed duration of effectiveness of cemiplimab from the original appraisal to align with the longer duration of follow up from EMPOWER-CSCC 1 and updated the quality-of-life data with the most recent data cut. The company model used the baseline characteristics from the company trials in its base case. However, after technical engagement, the company updated the baseline characteristics to those from the SACT dataset. This aligned with the ERG's preference, as this reflects the population who had cemiplimab in NHS practice. The company presented cost-effectiveness estimates for cemiplimab compared with chemotherapy and best supportive care. However, because best supportive care was agreed as the most appropriate comparator in this appraisal (see section 3.2), the cost-effectiveness results for cemiplimab compared with chemotherapy were not discussed further. The committee concluded that the company model is suitable for decision-making.

Survival extrapolations for cemiplimab and best supportive care are highly uncertain, but cemiplimab is likely to extend survival

3.9 The ERG noted that there is a high degree of uncertainty in the survival extrapolations for cemiplimab and best supportive care, because of limitations in the data (see sections 3.4 to 3.6). The committee noted that the ERG used the same survival extrapolations as the company in its base case, and explored a range of alternative extrapolations in scenario analyses. The committee was not presented with the SACT overall survival Kaplan–Meier data for comparison against the results from the company's trials and the modelled extrapolations. The committee noted that overall survival data from the SACT dataset has been used in economic modelling in other appraisals. The committee agreed that a scenario analysis using the overall survival estimates from the SACT Kaplan–Meier curve would have been helpful to quantify the uncertainty of the survival estimates for cemiplimab, given the lower overall survival in the SACT dataset than in the clinical trials. The committee concluded that the survival extrapolations for cemiplimab and best supportive care are highly uncertain. However, despite the uncertainties, the committee agreed that it was likely that cemiplimab did extend survival, although the extent to which is uncertain.

End of life

Cemiplimab for advanced unresectable CSCC meets the end of life criteria

3.10 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. In the company's and ERG's base-case analysis, the mean life expectancy for people receiving best supportive care was 1.42 life years. The committee also noted that the median life expectancy of people receiving best supportive care in the Sun et al. (2019) study was 5 months. The committee was satisfied that the life expectancy in this population was less than 24 months, despite the uncertainty in the evidence base for best supportive care. It was also satisfied that cemiplimab offers at least a 3-month life extension, based on the

evidence from the SACT dataset and the clinical trials, despite the uncertainties. Therefore, the committee concluded that cemiplimab for advanced CSCC that cannot be removed with surgery (unresectable) or cured with radiotherapy meets the end of life criteria.

Cost-effectiveness estimates

The cost-effectiveness estimates for cemiplimab are uncertain but are likely to fall within what NICE considers an acceptable use of NHS resources

3.11 At technical engagement, the company accepted the ERG's preferred assumptions in its base case. Both the company's and the ERG's base-case incremental cost-effectiveness ratio (ICER) for cemiplimab compared with best supportive care was £30,952 per quality-adjusted life year (QALY) gained. All the ICERs from the company and ERG scenario analyses were lower than £50,000 per QALY gained. The committee noted the significant uncertainty around the clinical effectiveness of cemiplimab in the NHS (see section 3.5) and that overall survival from the SACT dataset had not been used in the economic modelling (see section 3.9). The committee was also aware of the substantial uncertainty surrounding the comparator data for best supportive care and the indirect comparison (see sections 3.6 and 3.7). The committee considered its conclusion that the end of life criteria were met for cemiplimab. Because of the high level of uncertainty in the clinical evidence, the committee agreed that an acceptable ICER should be towards the lower end of the range normally considered a cost-effective use of NHS resources. Taking all of this into account, the committee concluded that cemiplimab was an acceptable use of NHS resources.

Other issues

Innovation

3.12 Cemiplimab is considered innovative because it potentially provides a

new treatment option for people who currently have limited access to any life-extending treatment. Cemiplimab is therefore considered a step-change in the treatment of advanced CSCC that cannot be removed with surgery or cured with radiotherapy.

Equalities

3.13 No equality issues were identified.

Conclusion

Cemiplimab is recommended for routine use

3.14 The committee concluded that, while there is significant uncertainty in the survival estimates for cemiplimab and best supportive care, the most likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. Therefore, cemiplimab is recommend as an option for treating metastatic or locally advanced cutaneous squamous cell carcinoma in adults when curative surgery or curative radiotherapy is not appropriate, if it is stopped at 24 months, or earlier if disease progresses.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has metastatic or locally advanced CSCC and the doctor responsible for their care thinks that cemiplimab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Lizzie Walker
Technical lead

Joanna Richardson
Technical adviser

Rebecca Richardson
Project manager

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