NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma

1 Recommendations

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

1.2 Treatment with cemiplimab should be continued until disease progression or for up to 24 months (whichever is sooner).

1.3 These recommendations are not intended to affect treatment with cemiplimab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Living with advanced unresectable cutaneous squamous cell carcinoma is physically and emotionally challenging, and there is a high unmet need for new treatments. Cemiplimab trial data are promising but uncertain.

The cost-effectiveness estimates for cemiplimab are above what is normally considered a cost-effective use of NHS resources. The evidence

on life expectancy with current treatments and how long life might be prolonged with cemiplimab is very uncertain. Because of this it is not known for certain whether the end-of-life criteria apply. So cemiplimab cannot be recommended for routine use in the NHS.

However, if more mature data become available from an ongoing trial of cemiplimab, and more data on life expectancy with current treatments are obtained, this could confirm the expectation that the end-of-life criteria apply. If this is the case, there is plausible potential for cemiplimab to be a cost-effective treatment. Therefore, cemiplimab is recommended for use within the Cancer Drugs Fund.

2 Information about cemiplimab

Marketing authorisation	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	The recommended dose of cemiplimab is 350 mg every 3 weeks. Treatment may be continued until symptomatic disease progression or unacceptable toxicity. Administration is by intravenous (IV) infusion.
Price	£4,650 per 350 mg vial (1 treatment cycle). The cost for 1 year of treatment with cemiplimab based on the list price is £80,877 (all prices excluding VAT, company submission). The company has a commercial arrangement (managed access agreement including a commercial access agreement). 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 (section 6) considered evidence submitted by Sanofi, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The committee noted that technical engagement has reduced the uncertainty related to several issues, and agreed that:

- People with significant autoimmune disease or who have had a solid organ transplant are unlikely to be eligible for treatment with cemiplimab.
- Cemiplimab is likely to be an appropriate treatment option for many people who would currently be offered chemotherapy. It is also likely to be an appropriate treatment option for some people who would currently be offered best supportive care. Therefore, chemotherapy and best supportive care are both relevant comparators.
- The company has pooled the data from 2 ongoing single-arm trials of cemiplimab with small patient numbers into a single 'integrated analysis'. There is a lot of uncertainty about the clinical effectiveness of cemiplimab (see section 3.3 and section 3.4), however, the pooling of data from the 2 studies is, in principle, acceptable, even though there are differences between the populations. This is because it allows a larger treated population to be analysed.
- It is acceptable that in the model adverse-event rates are informed by the frequency of grade 3 and 4 adverse events in the integrated analysis population, rather than the wider safety population for whom data were also reported.
- It is acceptable that the disutilities associated with adverse events are applied assuming a 1-month duration of effect for all adverse events.
- The company's updated estimates of resource use in the pre-progression health state are acceptable.

The committee recognised that there are remaining areas of uncertainty associated with the analyses presented (see the technical report, table 1 [pages 3 to 8] and table 3 [page 51]) and took this into account in its decision making.

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 both 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 the disease reaches an advanced state (locally advanced or metastatic) that cannot be removed with surgery (unresectable) or cured with radiotherapy. Often, people with advanced disease are older and have a poor prognosis. The skin lesions may grow 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. The patient experts explained that advanced CSCC can be extremely debilitating because it can result in unpleasant foul-smelling wounds that need daily dressings. Depending on the location and extent of the disease it can also cause pain. Living with advanced unresectable CSCC is challenging and, because of the visibility of the disease, it often results in people avoiding social interaction. The patient experts also noted that 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 patients and carers.

There is a high unmet need for new treatments for advanced unresectable CSCC

3.2 There is no established treatment pathway for advanced unresectable CSCC. The clinical experts noted that some patients have platinum chemotherapy, which is associated with a high risk of significant adverse events and has limited efficacy. Few patients have more than 3 cycles of therapy. The patient experts and the clinical experts agreed that amongst patients for whom chemotherapy is considered an option, the decision to proceed with treatment is often informed by patient preference. Some people choose best supportive care to avoid the toxic effects of chemotherapy. The clinical experts explained that chemotherapy is not an option for many people and, for them, treatment is limited to best

supportive care. The committee concluded that there is a high unmet need for new treatments for people with advanced unresectable CSCC.

Clinical evidence

The cemiplimab trial data are likely to be generalisable to the UK population but there are some key uncertainties

3.3 Data on response and survival outcomes for cemiplimab were reported in 2 single-arm trials. A key issue is the dosing regimens. All 26 patients in the phase I trial, and 123 of the 167 patients in the phase II trial, had a weight-based dose of 3 mg/kg of cemiplimab every 2 weeks. These 26 and 123 patients make up the base-case integrated analysis population. Data for people who had the anticipated licensed fixed-dose regimen of 350 mg every 3 weeks are limited to 44 patients in the third group of the phase II trial, all of whom had metastatic disease. This group has shorter follow up than the other 2 groups because of differences in the recruitment schedules. The committee compared the base-case results for patients who had the weight-based dose with the results of the company's scenario analysis which included patients who had the fixed dose. It recognised that small patient numbers in the fixed-dose group means that the scenario analysis is likely to be inconclusive and accepted that this is an area of uncertainty. The committee also noted expert opinion that the mean age of patients in the trials is probably lower than the average age of the patient population presenting with advanced disease in clinical practice. However, the experts explained that patients who are most likely to benefit from treatment (those with good performance status) are likely to be younger than the average age of people with advanced unresectable CSCC. Patients enrolled in the cemiplimab trials had Eastern Cooperative Oncology Group (ECOG) performance scores of 0 to 1. The committee also noted that 26 patients included in the base-case integrated analysis had treatment for up to 11 months but the remaining 123 patients had treatment for 22 months. The anticipated marketing authorisation does not include a stopping rule for

the maximum duration of treatment, but the clinical lead from the Cancer Drugs Fund explained that stopping rules are used in clinical practice for this type of treatment. The committee concluded that the trial data are likely to be generalisable to the NHS, but recognised that some uncertainty remains.

Cemiplimab trial data is promising but uncertain

3.4 The committee noted that the overall response rates reported in the trials are very promising. The overall response rate reported in the original company submission for the phase I trial is 50% (95% confidence interval 29.9 to 70.1) and the results for the phase II trial are similar. The committee also noted that median progression-free survival results in the phase II trial at the most recent analysis are favourable, and that median overall survival has not been reached in either trial, which suggests a promising treatment benefit. The clinical experts commented that these data suggest that cemiplimab is likely to be considerably more effective than chemotherapy, and that the adverse events appear similar to other immunotherapies. They explained that immunotherapies are generally better tolerated than chemotherapy. Taking the potential benefits and risks into account the clinical experts considered that, for eligible patients, cemiplimab would be a better option than chemotherapy or best supportive care. However, the committee noted the uncertainties related to generalisability of the data, and that the data come from single-arm trials with no comparator arm (see section 3.3, section 3.5 and section 3.6). Also, the trial data are immature. At the most recent data cut, more than 70% of patients in the phase II trial were still alive, so the duration of treatment effect and overall survival with cemiplimab is still unknown. The committee concluded that the evidence for cemiplimab compared with current care is promising but uncertain.

There is no reliable evidence for either of the relevant comparators

3.5 Comparator data are extremely limited. In the company's base case, the estimates of clinical effectiveness for both chemotherapy and best

supportive care are based on a sub-set of 18 patients who had platinum-based chemotherapy in a non-UK retrospective chart review (Jarkowski et al. 2016). In its original submission, the company provided a scenario analysis in which the clinical-effectiveness estimates for best supportive care were informed by pooled data from 4 studies of EGFR inhibitors (146 patients). After the company submitted their original submission another non-UK retrospective review (Sun et al. 2019) was published that included a sub-set of 36 patients with unresectable skin lesions on the head and neck. The clinical experts were concerned that the Jarkowski et al. 2016 data suggest more prolonged survival than is typically seen in their clinical experience with chemotherapy. They suggested that the study by Sun et al. 2019 provides a potentially more reliable estimate of life expectancy for patients having best supportive care. The committee was concerned that the Jarkowski et al. 2016 data does not appear to align with NHS experience and that the results may be unreliable because of the very small sample size, differences in patient selection and a non-UK population. It noted that similar limitations in the study design, population and sample size also apply to the Sun et al. 2019 data. The experts considered that the EGFR inhibitor data are not relevant to the NHS because this treatment is not licensed for use in the UK. The committee concluded that none of the data presented provide a reliable estimate of clinical outcomes for chemotherapy or best supportive care.

New evidence is expected to become available for both comparators that will provide a more suitable basis for decision making

3.6 The committee noted that the company is carrying out a retrospective chart review of patients who have had existing treatments in the UK. The committee recognised the limitations of the study design but noted the low probability of any controlled clinical trial data becoming available in the future. The committee concluded that the data from the chart review will be subject to considerable uncertainty, but the larger sample size and inclusion of 106 UK patients means that it would offer an additional and potentially better source of comparator data. The committee heard from

one of the clinical experts about a recently established keratinocyte cancer registry for basal cell carcinoma and CSCC. The clinical expert considered that the registry might be used to track the natural history of unresectable CSCC in the UK, potentially offering another source of comparator data. The committee considered that such data would potentially be of value but recognised that the precise mechanism for collecting and collating the appropriate data is currently unclear.

Indirect comparisons

None of the indirect comparisons provide a reliable estimate of relative effectiveness

3.7 Because the only available evidence is from 2 single-arm studies, an indirect treatment comparison (ITC) was needed. The company explored 3 ITC methods:

- a naive comparison (which fitted survival extrapolations directly to the observed data)
- a simulated treatment comparison (STC)
- a matching-adjusted indirect comparison (MAIC).

The committee noted the ERG's comments that the company's approach to the ITC is systematic and in line with the recommendations in the technical support document (TSD 18) published by NICE's Decision Support Unit. It acknowledged the company's decision to use the results of the naive comparison, which provide the least favourable estimates for cemiplimab, to inform the base case. But it noted that naive comparisons are methodologically inadvisable because outcomes are likely to be confounded by population differences between studies. It concluded that all 3 ITCs are based on comparator data that are considered unreliable (see section 3.6) and, therefore, the relative-effectiveness estimates for cemiplimab are highly uncertain regardless of which ITC method is used.

The company's economic model

The structure of the company's model is appropriate but some of the key inputs and assumptions are very uncertain

3.8 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 cycle length of 30.4 days with a half-cycle correction. The committee considered that the structure of the model is acceptable and in line with models used in other NICE appraisals. It noted, however, that some of the key clinical inputs and assumptions in the company's base case are very uncertain:

- The characteristics of the patients in the model, including age at baseline, may not completely represent patients who would have cemiplimab in UK clinical practice (see section 3.3).
- For the base case, the company assumed that patients will only have treatment for 24 months and that the treatment benefit of cemiplimab will last for 3 years in total (at this point the hazards for cemiplimab become equal to those used in the chemotherapy arm). The committee considered that these assumptions are not unreasonable given the effectiveness of other PD-L1 immunotherapies and clinical expert testimony, but it noted that the assumptions are not evidence-based and are therefore uncertain.
- The pre-progression utility is higher than estimates for the general population (adjusted for age and gender). This is inconsistent with the opinions of the patient and clinical experts, that patients living with advanced unresectable CSCC have a very reduced quality of life.
- The clinical experts noted that the overall-survival estimates used in the model, particularly for the comparator arm, do not align with their clinical experience. The committee was concerned about the lack of alignment but could not comment on the reliability of the modelled projections for overall survival because of the limitations in the data underpinning the extrapolations (see section 3.3 to section 3.7)

Cost-effectiveness estimate

The cost-effectiveness estimates for cemiplimab are very uncertain

3.9 The committee noted the significant uncertainty about the clinical effectiveness of cemiplimab compared with standard care in the NHS, particularly the issues related to using data from single-arm immature trials and the absence of any reliable comparator data. These uncertainties make the cost-effectiveness results highly uncertain. The committee also noted that the company's base-case incremental cost-effectiveness ratios (ICERs)are above what is normally considered to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained):

- The company's base-case ICER for cemiplimab is £45,693 per quality-adjusted life year (QALY) gained compared with chemotherapy, and £47,463 per QALY gained compared with best supportive care.
- The ICERs in all the scenario analyses are higher than £30,000 per QALY gained.

The committee concluded that the cost-effectiveness estimates for cemiplimab are not robust and therefore may or may not be within a range that could be recommended, even if the end-of-life criteria apply.

End of life

Cemiplimab might fulfil the end-of-life criteria, but this is uncertain

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. It noted that the cost-effectiveness evidence presented by the company does not support the application of the end-of-life criteria because the extrapolated life expectancy of patients in the comparator arm of the company's model exceeds 24 months. However, the committee noted the opinions of the clinical experts that the modelled survival estimates are not reflective of their clinical experience. The

committee concluded that it is possible that patients with advanced unresectable CSCC have an average life expectancy of less than 24 months, even though this is based on limited evidence. It also concluded that it is potentially plausible that cemiplimab will extend life by more than 3 months based on the currently available data, but these data are immature. The committee concluded that the end-of-life criteria might be met, but this is unproven at present. Because of uncertainty about the most plausible ICER, and about whether the end-of-life criteria are met, the committee was unable to recommend cemiplimab for routine commissioning.

Cancer Drugs Fund

The criteria for inclusion in the Cancer Drugs Fund are met

3.11 Having concluded that cemiplimab could not be recommended for routine use, the committee then considered if it could be recommended for treating advanced unresectable CSCC within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum).

- The company has expressed an interest in cemiplimab being considered for funding through the Cancer Drugs Fund.
- The key uncertainties in the data relate to:
  - the outcomes from current treatments in NHS clinical practice
  - the estimates of relative effectiveness for cemiplimab.
- If further data become available on outcomes in current NHS practice this will help to inform the relative effectiveness of cemiplimab compared with standard care, and also whether the 24-month end-of-life criterion is met. It could also provide information on the baseline characteristics of people who are likely to be offered cemiplimab, which would inform the baseline characteristics of the model cohort.

- More mature data from the cemiplimab trials will enable more robust ICERs to be calculated, and greater certainty about whether the 3-month extension to life criterion for end of life is met.
- Given the uncertainties in the current evidence, the committee did not state a preferred ICER but recognised that many of the assumptions in the company's base case appear reasonable and might be verified through further data collection.
- The committee concluded that cemiplimab meets the criteria to be considered for inclusion in the Cancer Drugs Fund.

Other issues

Innovation

3.12 Cemiplimab is considered innovative because it potentially provides a new treatment option for patients who currently have limited access to any life-extending treatment (see section 3.2). Cemiplimab is therefore considered a step-change in the treatment of advanced, unresectable CSCC.

Equalities

3.13 The committee discussed whether the compassionate-use criteria in the trials for cemiplimab reflect how it will be used in NHS practice. Specifically, the committee asked the clinical experts to comment on the criterion used in the company's compassionate-use programme that cemiplimab should not be offered to people with 'any acute or chronic psychiatric problems that, in the opinion of the physician, make the patient ineligible for participation'. The committee discussed whether this criterion would be used in clinical practice and potentially discriminate against people with disabilities as defined under the Equalities Act 2010. The clinical experts explained that in NHS practice people with CSCC and psychiatric problems would not be ineligible for cemiplimab, but acknowledged that some people, for example, those with advanced Alzheimer's disease, might have difficulty undergoing treatment, for example if they struggled with the requirement for regular intravenous

infusions. The committee concluded that people with disabilities, including those with learning disabilities or psychiatric disorders would not be disadvantaged by the recommendations, providing that clinicians act in the interest of their patients, in line with their usual responsibilities. The committee concluded that there was no need to alter or add to its recommendations in consideration of its duties under equalities legislation.

Conclusion

Cemiplimab is recommended for use within the Cancer Drugs Fund

3.14 The committee recommended cemiplimab for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic cutaneous squamous cell carcinoma in adults when curative surgery or curative radiotherapy is not appropriate, until disease progression or for up to 24 months (whichever is sooner). It is recommended only if the conditions in the managed access agreement for cemiplimab are followed.

4 Implementation

When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has 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 and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.1 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer

Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Date for review of guidance

5.1 The data collection period is expected to end in July 2021, when long-term overall survival and progression-free survival data for all 3 cohorts of the phase II trial are available. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

5.2 As part of the managed access agreement, cemiplimab will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in NICE's Cancer Drugs Fund methods guide (addendum).

Jane Adam
Chair, appraisal committee
April, 2019

6 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.

Juliet Kenny
Technical lead

Rufaro Kausi
Technical adviser

Thomas Feist
Project manager

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