

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination
**Avelumab for treating metastatic Merkel cell
carcinoma**

1 Recommendations

- 1.1 Avelumab is recommended as an option for treating metastatic Merkel cell carcinoma in adults, only if they have had 1 or more lines of chemotherapy for metastatic disease.
- 1.2 Avelumab is recommended for use within the Cancer Drugs Fund as an option for treating metastatic Merkel cell carcinoma in adults, only if:
- they have not had chemotherapy for metastatic disease and
 - the conditions in the managed access agreement for avelumab are followed.
- 1.3 This recommendation is not intended to affect treatment with avelumab 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

Treatment options for metastatic Merkel cell carcinoma are limited. People are usually offered chemotherapy or best supportive care. Avelumab could potentially be used as a first-line treatment or after chemotherapy.

Clinical trial evidence suggests that avelumab may improve overall survival compared with chemotherapy. But chemotherapy has not been compared directly with avelumab so the results are highly uncertain. The evidence on avelumab is promising, but the trial included only a small number of people and data are still being collected.

Avelumab as a first-line or second-line treatment meets NICE's criteria to be considered a life-extending end-of-life treatment.

Avelumab is recommended as a second-line treatment after chemotherapy because it is within the range NICE normally considers acceptable for end-of-life treatments. Avelumab has the potential to be cost effective as a first-line treatment, at the price agreed in the managed access agreement with NHS England. But more evidence is needed to address the clinical uncertainties. It is therefore recommended for use within the Cancer Drugs Fund as a first-line treatment while further data are collected.

2 The technology

Marketing authorisation indication	Avelumab (Bavencio, Merck) is indicated as monotherapy for 'the treatment of adult patients with metastatic Merkel cell carcinoma'.
Dosage in the marketing authorisation	10 mg/kg every 2 weeks by intravenous infusion over 60 minutes. Avelumab should be continued until there is disease progression or unacceptable toxicity. Patients could continue treatment if they have radiological disease progression that is not associated with significant clinical deterioration (defined as no new or worsening symptoms, no change in performance status for more than 2 weeks and no need for salvage therapy).
Price	£768 per 200 mg vial (excluding VAT; Monthly Index of Medical Specialities [MIMS] online [accessed January 2018]). The average cost of treatment per patient is £65,086 based on the list price. Costs may vary in different settings because of negotiated procurement discounts. In relation to recommendation 1.2, as part of the managed access agreement, the company has a commercial access agreement with NHS England. The financial terms of the agreement are commercial in confidence. The list price applies to 1.1.

3 Committee discussion

The appraisal committee (section 7) considered evidence submitted by Merck and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Merkel cell carcinoma

People with metastatic Merkel cell carcinoma would welcome avelumab as a treatment option

3.1 Merkel cell carcinoma is a rare and aggressive cancer with limited treatment options. There is an unmet clinical need for people with the disease. The patient experts explained that Merkel cell carcinoma often progresses rapidly, and can be frightening for both patients and families. The disease can start off as a small lump and then grow rapidly, spreading to other parts of the body (metastatic disease). Because it affects the surface of the skin, it is a very visible disease that can become

oozing and unsightly. When it spreads to other parts of the body, patients are currently offered chemotherapy if they are able to tolerate it. The initial response rates are relatively high, but the disease often relapses quite quickly. The main benefit of avelumab is the potential for both good response rates and longer disease control than is seen with chemotherapy. The patient experts stated that avelumab has shown very rapid responses in some cases, with fewer side effects than chemotherapy. The clinical experts indicated that avelumab could be used either as a first treatment or after chemotherapy, but should ideally be used as early as possible in the treatment pathway for maximum clinical benefit. The committee concluded that avelumab offers a promising treatment option for people with metastatic Merkel cell carcinoma.

Chemotherapy or best supportive care are appropriate comparators

3.2 The committee noted that the marketing authorisation for avelumab does not specify when it should be given in the treatment pathway (as the first treatment in metastatic disease or after chemotherapy). The clinical experts explained that they would like to offer avelumab to patients who have had none or only 1 previous line of therapy. The committee was aware that the final scope of this appraisal includes chemotherapy as a comparator for patients who have not had any treatment for metastatic disease (referred to as first line), and best supportive care for patients who have had 1 previous treatment (referred to as second line). The committee concluded that the appropriate comparator for first-line treatment is chemotherapy. However, it noted that some patients may be unable to have chemotherapy and are offered best supportive care instead. For second-line treatment, the committee concluded that best supportive care is the most appropriate comparator because very few patients would be expected to have chemotherapy again.

Clinical trial evidence

Results from the JAVELIN trial should be interpreted with caution

3.3 The evidence for avelumab came from JAVELIN. This is a single-arm non-randomised trial of patients with metastatic Merkel cell carcinoma. The trial has 2 parts:

- Part A: 88 patients with relapse after at least 1 line of chemotherapy ('second-line and beyond' group).
- Part B: 39 patients who had not had previous systemic therapy for metastatic disease (first-line group).

The company originally presented interim data from a cut-off date of March 2017, and explained that it is still collecting data for both part A and part B. In response to consultation, and in support of the original analyses, the company presented additional data from a cut-off date of September 2017 (these data are academic in confidence and are not reported here). The committee was concerned that the interim data from part B (first-line group) relies on a very small number of patients with a short follow-up (29 patients were followed for 3 months or more, 14 were followed for 6 months or more). Follow-up in part A (second-line and beyond group) was 18 months. The committee welcomed the availability of slightly more mature data based on a larger number of patients, but the further data did not overcome the issue that the results were from 1 single-arm non-randomised trial. The committee also noted that the marketing authorisation has been granted conditionally for the first-line group because of the immaturity of the data. The European public assessment report specifies that further data cuts are expected to provide additional evidence on efficacy and toxicity. The committee concluded that the JAVELIN results should be interpreted with caution.

There are some unanswered questions about the generalisability of the JAVELIN results

3.4 The committee discussed the baseline characteristics of patients in the JAVELIN trial:

- Patients who were immunosuppressed were excluded from the trial. The clinical experts stated that patients with neuroendocrine tumours are generally responsive to immunotherapies such as avelumab, including those who are immunosuppressed. They stated that the only people who are immunosuppressed who may not be offered avelumab would be patients who have had a transplant, and this would be because of the risk of rejection rather than because avelumab would be less effective. There are some people, for example, with chronic lymphatic leukaemia or on very high doses of corticosteroids, who may not do well on this treatment. However, this would be very few patients and would be assessed on an individual basis. The committee agreed that although patients who were immunosuppressed were excluded from the trial, most could have been offered avelumab.
- There were no study sites in England and the median age of the patients in part A was 72.5 years, which is slightly older than that expected in clinical practice in England (70.0 years).
- The overall survival data may be confounded by the use of subsequent treatments, and no data on subsequent treatments were recorded as part of the trial.
- The Eastern Cooperative Oncology Group (ECOG) performance score of patients was 0 to 1 in the trial. The clinical experts stated that, in clinical practice, they would offer immunotherapy to some patients who have an ECOG score of 2, if this was because of unrelated comorbidities that would not affect their ability to tolerate or benefit from avelumab. The clinical experts also stated that if patients have an ECOG score of 2 because of advanced Merkel cell carcinoma then immunotherapy may not be appropriate because patients need to have a reasonable life expectancy to be able to benefit from immunotherapy.

The committee concluded that there were some unanswered questions about the generalisability of the trial to UK clinical practice.

Clinical-effectiveness results for avelumab in second and further lines of treatment are promising but should be interpreted with caution

3.5 JAVELIN showed favourable efficacy outcomes for avelumab when used as a second or subsequent treatment (objective response rate of 33% at 18-month follow-up). The clinical experts explained that avelumab, as an immunotherapy agent, is expected to produce a more durable response than chemotherapy. The committee also heard that this durable progression-free survival should result in longer overall survival. It noted that the median overall survival was 12.6 months, which was higher than would currently be expected for patients with metastatic Merkel cell carcinomas. Even taking into account the later September 2017 data, the committee noted that the overall survival data were still relatively immature. It concluded that, although there were uncertainties, the results for avelumab used in second and further lines were very promising.

Clinical-effectiveness results for avelumab as a first-line treatment are promising but should be interpreted with caution

3.6 The median overall survival for first-line treatment had not been reached, but JAVELIN showed promising response rates for avelumab as a first-line treatment. The clinical expert explained that the first-line response rates in JAVELIN had been high so far (62.11% at 3 months and 71.40% at 6 months for overall objective response rate). Taking into account the September 2017 data, the clinical experts anticipate that the response rate first line should be at least equal to, and possibly slightly better, than in second-line treatment. However, the committee was concerned that the results were from a very small number of patients with a short follow-up, and that data on progression-free and overall survival were not adequate for decision-making. It noted that the trial provided no direct comparison with any other treatment and that data collection is ongoing in JAVELIN for first-line use. The committee concluded that the results for first-line use

in metastatic Merkel cell carcinoma are highly immature and should be interpreted with caution.

Naive indirect comparison

Observational data are appropriate for comparison with JAVELIN

3.7 JAVELIN is a single-arm trial with no comparator, so the company did a naive (that is, unadjusted) indirect comparison of avelumab against chemotherapy using a retrospective observational study of patients with metastatic Merkel cell carcinoma (study 100070-Obs001). The company did this study specifically for the purpose of comparing avelumab with chemotherapy. The study has 2 parts:

- Part A, done in the United States (US): 67 patients who had systemic chemotherapy first line, and 20 patients who had systemic chemotherapy after at least 1 line of chemotherapy.
- Part B, done in the European Union: 34 patients who had systemic chemotherapy after at least 2 previous lines of chemotherapy.

The committee concluded that, given the lack of data for this disease, the 2-part observational study was appropriate for comparison with JAVELIN.

The results from the naive indirect comparison are highly uncertain

3.8 The naive indirect comparison suggests that, for both first line and second and further lines, avelumab has improved overall response rates, progression-free survival and overall survival compared with chemotherapy. The ERG considered that results from JAVELIN and the 2-part observational study should have been adjusted for differences in baseline characteristics including immunosuppression, ECOG performance score and age. In its clarification response, the company did regression analyses for the second-line and beyond group, but the ERG still had concerns with these analyses. The committee recalled the immaturity of the data and the small patient numbers, particularly first line. The committee heard from the ERG that, because efficacy data were only

from non-randomised single-arm studies, it could not accurately assess how avelumab compares with chemotherapy or best supportive care. The committee concluded that the results from the naive indirect comparison should be interpreted cautiously.

Adverse events

Avelumab has an acceptable tolerability profile

3.9 The clinical experts explained that immunotherapy agents such as avelumab are generally better tolerated than chemotherapy, but immune-related adverse reactions can occur. The committee noted that no treatment-related deaths were recorded in JAVELIN, but treatment-related adverse event rates were high in both the first-line and second-line groups (71.8% and 75.0% of patients respectively). The committee would have liked to have seen long-term safety data but it appreciated that further data are being collected. The committee concluded that avelumab is generally better tolerated than chemotherapy but it can cause immune-related adverse reactions.

The company's economic model

The company's model structure is appropriate for decision-making

3.10 The company presented a 3-state partitioned survival model comparing avelumab with chemotherapy or best supportive care in patients having first-line treatment, and comparing avelumab to best supportive care in patients having second and further lines of treatment. Each model included 3 health states (progression-free disease, progressed disease and death) with 3 sub-health states (greater than 100 days until death, 30 days to 100 days until death, and less than 30 days until death). The sub-health states applied to both the progression-free and progressed disease health states, and accounted for the deterioration in health-related quality of life when a patient approaches death. Although uncommon, the ERG considered this approach to be reasonable to capture the changes in quality of life that patients experience over their

lifetime, in addition to the changes experienced after progression of the disease. The committee concluded that the model structure was appropriate for decision-making.

Progression-free survival and overall survival estimates

The modelled progression-free and overall survival for second and further lines of treatment is uncertain

3.11 The committee first discussed the second and further lines of treatment model, being aware that first-line survival estimates were developed and derived from the second- and further-line modelling. In its second- and further-line model, the company used a spline-based approach (a flexible parametric survival method) to extrapolate progression-free and overall survival estimates for the time horizon of the model. Because the tail observed for progression-free survival was long (suggesting a durable response), the company censored patients at 18-month follow-up. This allowed the progression-free survival estimate not to be overly influenced by a potentially optimistic estimate of durable response. The committee decided that this method was reasonable. However, it noted that the estimates were based on a naive indirect comparison with small numbers of patients (see section 3.7) and an extrapolation from 18 months of follow-up to a 40-year time horizon, and were therefore highly uncertain. Because of the limitations of the naive comparison the ERG preferred a Weibull regression, adjusting for parameter differences (including immunosuppression, age and gender) between study 100070-Obs001 and JAVELIN. The committee concluded that it was not possible to confidently decide which method produced the more reliable results.

The survival estimates for first-line treatment are highly uncertain

3.12 Because of the very limited data for first-line treatment (see section 3.6), the company considered it was unreliable to use progression-free and overall survival trial data in the first-line model. Instead, it used estimates derived from the second-line and beyond model in its original first-line model. The committee was concerned that the progression-free and

overall survival estimates for first-line treatment were based on clinical assumptions, not direct evidence. The ERG considered that it was more appropriate to fit distributions for avelumab to the first-line estimates, rather than generating survival curves dependent on the second-line and beyond estimates and relying on assumptions. The committee was aware that the ERG's preferred survival model did not solve the issue of the uncertainty caused by limited data. The committee heard from the ERG that the company's original cost-effectiveness result for first-line treatment was most sensitive to the hazard ratio chosen for overall survival. The committee concluded that the company's original progression-free and overall survival estimates for first-line treatment with avelumab are highly uncertain.

The effectiveness of best supportive care is assumed to be equivalent to chemotherapy

3.13 The company used patient-level data from the 2-part observational study 100070-Obs001 to estimate progression-free and overall survival for chemotherapy. The effectiveness of best supportive care was assumed to be equivalent to chemotherapy. The committee noted that the company used chemotherapy as a proxy for best supportive care in both first-line and second-line and beyond treatment because of a lack of data for best supportive care. In the second-line and beyond population, the company used pooled patient-level data from part A and part B to estimate progression-free and overall survival for chemotherapy. In the first-line population, the company used data from part A to estimate progression-free and overall survival for chemotherapy. The committee noted that there were no direct comparative data, and concluded that, although uncertain, the 2-part observational study 100070-Obs001 provided the most appropriate comparator data.

Time-on-treatment estimates

The company's assumptions for modelling time-on-treatment are in line with clinical practice

3.14 The company assumed that two-thirds of patients would stop treatment after 2 years (and all remaining patients would stop treatment after 5 years). The clinical experts explained that they expect 95% of patients having avelumab to stop treatment by 2 years. They explained that, for many immunotherapies used in other diseases, when there is a durable response and patients remain well, treatment tends to be stopped by 2 years. At this point, many patients would not want to keep coming back for further treatment. The clinical experts stated that there may be patients with a large volume of disease that was continuing to improve, who may wish to continue on treatment beyond 2 years, but this would be very few patients. The ERG noted that this assumption could potentially underestimate treatment costs. It considered the time-on-treatment extrapolation without truncation at 2 years to be more plausible and therefore included this approach in its base case. The committee agreed that the company's assumptions appeared to reflect clinical practice with regard to stopping treatment. However, it concluded that it would consider both the company's and the ERG's assumptions in its decision-making.

Utility values in the economic model

The baseline utilities are high

3.15 JAVELIN collected health-related quality-of-life data using EQ-5D-5L and FACT-M questionnaires. The company mapped the EQ-5D-5L data to EQ-5D-3L values using a validated mapping function, in line with [NICE's position statement](#) on EQ-5D-5L. The company used a regression model to generate utilities from the mapped EQ-5D-5L. The utilities varied across 3 time periods relative to time of death: utility for greater than 100 days until death; utility for 30 days to 100 days until death; and utility for less than 30 days until death. The committee was aware that the utilities

included the effect of adverse reactions. The ERG noted that the company did not compare the utilities used in the model with those reported in the literature. The committee heard that the time-to-death and baseline utilities were higher than the age-matched UK population. The committee agreed that these values were implausibly high but it noted that, because the same utilities were applied regardless of treatment group, only the difference between health states mattered. The committee concluded that it could accept the company's utility values but acknowledged that these were very high.

The company's base case

The company's revised base-case results for second and further lines of treatment are similar to the ERG's revised base case

3.16 The company's original base-case incremental cost-effectiveness ratio (ICER) for avelumab compared with best supportive care was £37,350 per quality-adjusted life year (QALY) gained. However, the company's original base case did not include all of the committee's preferred assumptions, that is:

- using Weibull regressions to model progression-free and overall survival (see section 3.11)
- adding the cost of premedication (approximately £100).

At the request of the committee following the first committee meeting, the ERG submitted a revised base case that included the above assumptions, and incorporated the company's method for modelling time-on-treatment (which predicted 5.4% of patients having treatment with avelumab at 2 years). The ERG's revised base case resulted in an ICER of £37,629 per QALY gained compared with best supportive care. Following the consultation, the company submitted a revised base case with:

- added administration costs (approximately £43)

- an assumption that only 5.0% of patients have treatment with avelumab at 2 years.

The revised base case resulted in an ICER of 37,846 per QALY gained compared with best supportive care. The company explained that no further data collection is planned for part A of JAVELIN, and noted that second and further-line treatment data were mature. The ERG noted minor differences in the estimates for patients still having treatment at 2 years, and in premedication costs. However, the ERG agreed with the company that JAVELIN part A data are mature, and noted that the company's revised ICER of £37,846 was very close to the ERG's revised base case of £37,629 per QALY gained. Despite this, the ERG highlighted that the revised estimate was still based on uncertain clinical parameters. The committee was concerned about the limited follow-up on overall survival, and it was unclear why the company did not plan to collect further data. The committee was also concerned about the uncertainties in the clinical data (see section 3.5), particularly the small number of patients and the limitations of the naive comparison (see section 3.7), and about the reliability of the long-term modelling results (see section 3.11). However, the committee concluded that an ICER of around £38,000 per QALY gained was plausible.

The company's revised first-line base-case results are based on immature data, which are highly uncertain and differ from the ERG's estimate

3.17 The company's original base-case ICER for avelumab compared with chemotherapy was £43,553 gained. However, the company's original base case did not include all of the committee's preferred assumptions, that is:

- using the parametric curves to model progression-free and overall survival (see section 3.12)
- adding the cost of premedication (approximately £100).

The ERG submitted a revised base case, as requested by the committee following the first committee meeting. This included the above assumptions and the company's method for modelling time-on-treatment, resulting in 8.5% of patients still having treatment with avelumab at 2 years. The ERG's revised base-case ICER was £72,033 per QALY gained compared with chemotherapy. Following consultation, the company submitted a revised base case in which it:

- added administration costs (approximately £43)
- corrected an error in the calculation of background mortality
- assumed that only 5% of patients have treatment with avelumab at 2 years
- adjusted the ERG's progression-free and overall survival modelling because first-line hazards were larger than second and further-line treatment hazards, and the company considered it unlikely that avelumab is less effective first line than when given later in the course of the disease.

The revised company base case resulted in an ICER of £58,315 per QALY gained compared with chemotherapy, lower than the ERG's base case of £72,033 per QALY gained. The assumption that only 5% of patients have treatment with avelumab at 2 years (a decrease from 8.5%) resulted in a decrease of approximately £5,000 per QALY gained from the ERG's revised base-case ICER. The ERG reiterated that 5% may be too low and may underestimate the cost of treatment (see section 3.14). The ERG also commented that the cost of premedication included in the company's new base case was less than the committee's estimate of £100. On the issue of first-line hazards, the ERG agreed with the company that the first-line hazards should not be larger than second-line and beyond hazards; that is, the effectiveness of avelumab would not be less when given first line compared with later in the disease. However, the ERG highlighted that the progression-free and overall survival modelling are both highly uncertain because of the lack of clinical data. The

committee agreed with the ERG on that point and was very concerned about the lack of clinical data, particularly the very small number of patients in part B of JAVELIN, and the uncertainties around the methods used to generate the survival estimates. It agreed that the most plausible ICER is highly uncertain, and considered that the first-line evidence will be strengthened when the company can present further clinical data based on a larger number of patients with longer follow-up. The committee concluded that the most plausible ICER could be between £58,000 and £72,000 per QALY gained, although it could also be above or below this range.

End-of-life

Avelumab meets the end-of-life criteria

- 3.18 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#).
- 3.19 The committee noted the evidence presented by the company for first-line treatment. Based on the median overall survival from the US part A observational study (100070-Obs001), the life expectancy of people with metastatic Merkel cell carcinoma was estimated to be 11.5 months. The modelled mean value was closer to 24.0 months, but it was based on very uncertain extrapolations of overall survival with first-line treatment. The trial evidence showed considerably longer survival with avelumab compared with current NHS treatment. The committee concluded that avelumab meets the criteria to be considered a life-extending end-of-life treatment for first-line treatment of metastatic Merkel cell carcinoma.
- 3.20 The evidence presented by the company indicated that people with metastatic Merkel cell carcinoma on second and further-line treatments have a life expectancy of between 5.1 months and 5.5 months, and that avelumab extends life by at least an additional 3 months compared with current NHS treatment. The committee accepted that avelumab meets the

end-of-life criteria for second-line treatment of metastatic Merkel cell carcinoma.

Cost-effectiveness estimates

Avelumab can be recommended for routine commissioning for second-line and beyond treatment

3.21 The committee considered the company's new base-case ICER of £37,846 per QALY gained, and the ERG's revised base-case ICER of £37,629 per QALY gained. It noted that, although these are within the range that could be considered cost effective for end-of-life treatments, both estimates are uncertain. The committee recalled that no new data are being collected in part A of JAVELIN (see section 3.16) and therefore the uncertainty is unlikely to be resolved further. The committee agreed that avelumab is a promising treatment option for people with metastatic Merkel cell carcinoma, which is a very rare disease (see section 3.1), and heard from the clinical experts that only a very small number of people would be offered avelumab second line, particularly if it were available for first-line use. The committee agreed that a degree of uncertainty was acceptable in these circumstances, and was persuaded that avelumab is a clinically- and cost-effective treatment for people with metastatic Merkel cell carcinoma when used second line and beyond. It therefore recommended avelumab for routine use in the NHS for this population.

Avelumab cannot be recommended for routine use in the NHS for first-line treatment because the clinical and cost effectiveness is highly uncertain

3.22 The committee considered the company's new base-case ICER of £58,315 per QALY gained, and the ERG's revised base-case ICER of £72,033 per QALY gained. It noted that both estimates are above the range that could be considered cost effective for end-of-life treatments. The committee agreed that, because of the uncertainty in the evidence, it was difficult to determine a robust cost-effectiveness estimate. It considered that both the company's and the ERG's revised estimates were potentially plausible, but that both were highly uncertain. The

committee concluded that avelumab had not been proven to be a cost-effective treatment for people with metastatic Merkel cell carcinoma when used first line, and it could not currently be recommended for routine commissioning in the NHS.

Cancer Drugs Fund

Avelumab is a promising first-line treatment and more data are needed to establish its clinical and cost effectiveness

3.23 Having concluded that avelumab could not be recommended for routine first-line use, the committee then considered if it could be recommended for treating metastatic Merkel cell carcinoma first line within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the [addendum to the NICE process and methods guides](#). The company confirmed in its consultation response that it would consider the option of a recommendation in the Cancer Drugs Fund.

Avelumab is suitable to be recommended for use in the Cancer Drugs Fund, when used first line

3.24 The range of ICERs for first-line treatment was £58,315 to £72,033 per QALY gained (see section 3.22). The committee considered that avelumab is a promising treatment, and that early use in the course of disease would be favoured by patients and clinicians. It acknowledged that immature data were used in the model, and that ongoing data collection in JAVELIN part B would reduce the uncertainty about the progression-free and overall survival benefit. There is plausible potential for first-line use of avelumab to be cost effective, if further trial data prove favourable. Therefore the committee concluded that avelumab is suitable to be recommended for use in the Cancer Drugs Fund, when used first line for people with metastatic Merkel cell carcinoma, while further trial data accrues.

Innovation

All potential quality-of-life benefits are accounted for in the committee's decision

3.25 The committee noted the company's view that avelumab has the potential to help address the considerable unmet clinical need of people with metastatic Merkel cell carcinoma who currently have limited treatment options available to them at end-of-life. The committee heard from the clinical and patient experts that avelumab is innovative in its potential to have significant and substantial clinical benefits. It understood that avelumab is generally well-tolerated compared with chemotherapy. The committee agreed that avelumab addresses an unmet need for a debilitating condition with few treatment options, but considered that the benefits had been adequately captured in the QALY calculations.

4 Implementation

Routine commissioning

- 4.1 Section 7(6) 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 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 determination.
- 4.3 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 Merkel cell carcinoma and has had 1 or more previous lines of therapy, and the doctor responsible for their care thinks that avelumab is the right treatment, it should be available for use, in line with NICE's recommendations.

Cancer Drugs Fund and a managed access agreement

- 4.4 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 metastatic Merkel cell carcinoma and has had no prior lines of therapy, and the doctor responsible for their care thinks that avelumab 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](#).
- 4.5 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 determination or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.
- 4.6 Avelumab has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Merck have a commercial access agreement that makes avelumab available to the NHS at a reduced cost for people who have not had chemotherapy for metastatic disease. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the

commercial access agreement should be directed to [\[NICE to add details at time of publication\]](#)

5 Recommendations for data collection

- 5.1 As a condition of the positive recommendation and the managed access arrangement, the company is required to collect efficacy data from the JAVELIN part B trial.

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review 3 years after publication or after the final analysis for JAVELIN part B is available, whichever is earlier. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.
- 6.2 The data collection period is expected to end in May 2019, when the final analysis of JAVELIN part B is available. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.
- 6.3 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund for first-line treatment 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 the [addendum](#) to NICE's methods and processes when appraising cancer technologies.

Jane Adam
Chair, appraisal committee
March 2018

7 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.

Aminata Thiam and Marcela Haasova

Technical Leads

Joanna Richardson

Technical Adviser

Thomas Feist

Project Manager

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