NICE National Institute for Health and Care Excellence

NICE guidance

Avelumab for untreated metastatic Merkel cell carcinoma

Technology appraisal guidance
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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.

Contents

This guidance partially replaces TA517.

1 Recommendation

1.1 Avelumab is recommended as an option for treating metastatic Merkel cell carcinoma in adults who have not had chemotherapy for metastatic disease. It is recommended only if the company provides avelumab according to the commercial arrangement.

Why the committee made this recommendation

This appraisal reviews the additional evidence collected in the Cancer Drugs Fund managed access agreement for avelumab for metastatic Merkel cell carcinoma in adults who have not had chemotherapy for metastatic disease (NICE technology appraisal guidance 517). The new evidence includes data from clinical trials and from people having treatment in the NHS while this treatment was available in the Cancer Drugs Fund in England.

Avelumab is routinely available in the NHS for treating metastatic Merkel cell carcinoma after chemotherapy. Evidence collected while avelumab was in the Cancer Drugs Fund shows that it is an effective treatment for untreated disease. It shows that, compared with chemotherapy, avelumab improves how long people have before their disease progresses and how long they live.

Avelumab is considered to be a life-extending treatment at the end of life. Cost-effectiveness estimates for avelumab are within what NICE consider an acceptable use of NHS resources. Therefore, it is recommended.

2 Information about avelumab

Marketing authorisation indication

2.1 Avelumab (Bavencio, Merck/Pfizer) is indicated as monotherapy for 'the treatment of adult patients with metastatic Merkel cell carcinoma'.

Dosage in the marketing authorisation

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

2.3 The licensed dose has changed since NICE's technology appraisal guidance on avelumab for treating metastatic Merkel cell carcinoma. The dosage given in the JAVELIN trial was 10 mg/kg. In November 2019, the approved dose was changed to the dose described in the summary of product characteristics.

Price

2.4 The list price of avelumab is £768 per 200-mg vial (excluding VAT; British National Formulary [BNF], accessed January 2021). The company has a commercial arrangement. This makes avelumab 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 Merck, a review of this submission by the evidence review group (ERG), NICE's technical engagement response form, and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need and treatment pathway

Metastatic Merkel cell carcinoma is a rare disease with limited treatment options

3.1 Patient groups explained in their written submissions that metastatic Merkel cell carcinoma is an aggressive and frightening cancer for patients. This fear stems from its visibility on the surface of the skin, the potential for disfigurement and rapid observable changes. Because its diagnosis is rare, clinical data and research are limited. This leads people to worry that decision making relating to future treatments and options will be impacted. Merkel cell carcinoma is currently treated with chemotherapy and best supportive care. However, chemotherapy is rarely effective and relapse rates are high with little sustained response. Because of the absence of alternative treatments, people often choose to have chemotherapy despite its limited effectiveness. Avelumab is already routinely used in metastatic Merkel cell carcinoma but only after chemotherapy. Earlier use of avelumab would offer people an alternative to chemotherapy. Benefits include a sustained response, fewer side effects and positive impact on quality of life. The patient expert present at the committee meeting also explained that avelumab makes a huge difference both physically and psychologically to people with metastatic Merkel cell carcinoma and their families. The committee concluded that there is a high unmet need for effective treatments in metastatic Merkel cell carcinoma and that early use of avelumab in the course of the disease would be welcomed by people with the disease and their families.

Clinical trial evidence from JAVELIN

Avelumab is an effective treatment for metastatic Merkel cell carcinoma

3.2 The clinical-effectiveness evidence came from JAVELIN, a single-arm open-label trial in people with metastatic Merkel cell carcinoma. The trial has 2 parts:

- Part A: people with disease relapse after at least 1 line of chemotherapy.
- Part B: people who had not had previous systemic therapy for metastatic disease.

The first-line cohort (part B) is relevant to this appraisal. The main clinical uncertainties identified by the committee in NICE's technology appraisal guidance on avelumab for treating metastatic Merkel cell carcinoma (from now on, referred to as TA517) were the small numbers of people in the cohort, the short follow up and the immaturity of the progression-free survival (PFS) and overall-survival (OS) data. The committee concluded that more mature OS data from JAVELIN part B would be likely to resolve uncertainty around the treatment effect of avelumab and allow more reliable cost-effectiveness estimates. This appraisal reviews the most recent data from JAVELIN part B, which includes 116 people and has a median follow up of 16 months. The results show a median OS of 20 months, and a median PFS of 4.1 months. OS at 6 months was 75%, decreasing to 60% at 12 months. PFS at 6 months was 41%, decreasing to 31% at 12 months. The committee concluded that the mature data from JAVELIN show that avelumab is an effective treatment for metastatic Merkel cell carcinoma in people who have not had previous systemic therapy for metastatic disease.

JAVELIN is generalisable to UK clinical practice

3.3 The committee discussed the baseline characteristics of people in JAVELIN part B. The ERG's commented that, compared with clinical practice, the population may be slightly younger, and include more men and people with more favourable Eastern Cooperative Oncology Group (ECOG) performance scores. Professional and patient groups at technical

engagement also commented that the trial population broadly resembles people in clinical practice, but with more men and a higher than expected proportion of people with an ECOG score of 0 (meaning they are fully active). The clinical experts agreed that the trial population is broadly representative and explained that any differences between the trial and people who have treatment in clinical practice are not unique to metastatic Merkel cell carcinoma. These differences are seen in many cancers, as frailer people are generally excluded from cancer trials. The committee also heard from the company that the efficacy and safety outcomes from JAVELIN are similar to outcomes expected in the clinical setting. The committee concluded that the results from JAVELIN are generalisable to the NHS.

Clinical evidence from the systemic anticancer therapy (SACT) data

SACT provides an additional data source to support decision making

3.4 Observational data for patients in the Cancer Drugs Fund obtained from the SACT dataset were presented by the company but were not included in its economic analysis. However, the ERG used the SACT dataset in a scenario analysis. The SACT dataset includes 52 people and has a median follow up of 6 months. The results showed a median OS of 11.8 months. OS at 6 months was 58%, decreasing to 50% at 12 months. PFS data were not collected. The committee noted that there were several limitations with the SACT data compared with JAVELIN part B, including a smaller sample size (n=52 versus n=116), data immaturity (median follow up for OS is 6 months versus 16 months), and a reduced number of outcomes collected. The committee concluded that the SACT data are limited by these factors but could be used as an additional data source to support decision making.

Indirect treatment comparison of avelumab and chemotherapy

The ERG's adjusted analysis was preferred by the committee

3.5 In TA517, the company did a naive (that is, unadjusted) indirect comparison of avelumab against chemotherapy using a retrospective observational study of people with metastatic Merkel cell carcinoma (study 100070-Obs001). The company did this study specifically to compare avelumab with chemotherapy. For this appraisal, it updated its naive indirect comparison with the 2019 JAVELIN part B data. No new data for chemotherapy were identified. The results of the naive indirect comparison suggest that avelumab improves overall response rates, PFS and OS compared with chemotherapy. However, the ERG was concerned about the methodological robustness of using a naive unadjusted comparison. It noted that by using a naive pooled analysis of multiple chemotherapy studies, the company was likely to introduce unnecessary heterogeneity into the analysis. The ERG considered the use of the immunocompetent subgroup of study 100070-Obs001 more appropriate for a naive comparison with JAVELIN, as JAVELIN only includes people who are immunocompetent. However, the ERG noted that this approach is still potentially unreliable. At clarification, the ERG requested that the company perform propensity score weighting analysis to compare avelumab with chemotherapy efficacy using JAVELIN part B and study 100070-Obs001. The ERG's preferred analysis adjusted for age, sex and ECOG performance score and maintained all patients in the analysis while achieving the best balance in baseline characteristics. The committee agreed with the ERG that an adjusted analysis was more appropriate than a naive comparison.

Cost effectiveness

The company's updated model uses the committee's preferred assumptions

3.6 The committee considered the preferred committee assumptions from

TA517. It recalled that the cost-effectiveness estimates were largely dependent on the modelling of PFS and OS, which were uncertain because the trial data were immature. The committee had concluded that there was a plausible potential for avelumab to be cost effective, and that further clinical data from JAVELIN based on a larger number of people with longer follow up could reduce the uncertainty and produce more reliable cost-effectiveness estimates using the original economic model. The ERG explained that the model structure remained the same and was generally in line with the committee's preferred assumptions. The committee was satisfied the company had adhered to the preferred assumptions from TA517.

The modelling of OS is appropriate

3.7 To estimate the expected overall survival for avelumab, the company used a 1-knot odds spline-based model. The ERG considered a 1-knot spline-based model to be appropriate but preferred the 1-knot hazard spline. It highlighted that uncertainties in the naive comparison of the treatment effects of avelumab with chemotherapy meant that a more conservative approach using the hazard-based 1-knot spline was appropriate. After technical engagement, the committee heard from the company that all 3 of the 1-knot modelling approaches produced estimates in line with clinical advice. Each curve produced was also a near-identical fit to the Kaplan-Meier curve. The company explained that the ERG's preferred 1-knot hazard spline, when extrapolated, eventually resulted in an estimated hazard of death that exceeds that of the base-case analysis in TA517 for people who have had 1 or more lines of chemotherapy. This does not align with clinical opinion that a treatment-naive population has better outcomes than those who have had chemotherapy. The ERG acknowledged that all 3 of the 1-knot models presented by the company are very similar and, on its own, the selection of model is unlikely to make a difference to decision making. The committee agreed with the ERG's comments and concluded that the modelling of OS is appropriate for decision making.

The modelling of PFS is appropriate

3.8 To extrapolate PFS for avelumab, the company used a 2-knot odds

spline-based model. The ERG noted that the 2-knot odds spline-based model underestimated the Kaplan-Meier data between 0.5 and 1 year and overestimated the Kaplan-Meier data for the tail. The ERG considered the 3-knots odds spline to provide a better extrapolation as well as a better fit to the data. After technical engagement, the company commented that there was little evidence to reject one model in favour of the other, and that both models are suitable for decision making with limited impact on the incremental cost-effectiveness ratio (ICER). The committee agreed with these comments and concluded that the modelling of PFS is appropriate for decision making.

The modelling of time on treatment is appropriate

3.9 To extrapolate time on treatment for avelumab, the company used Weibull curves. Extrapolation beyond the minimum follow-up period of 15 months in JAVELIN part B was informed by data from JAVELIN part A (people with relapse after at least 1 line of chemotherapy), in which the minimum follow up was 36 months. Clinical experts advising the company expected most people to stop avelumab within 2 years of initiation, and it was assumed in the model that people remaining on treatment at 5 years would immediately stop. The ERG agreed with this assumption and used it in its preferred analyses. However, the ERG did not agree that the curves fitted to the time-on-treatment data should be adjusted using the JAVELIN part A data, as these data are not reflective of a treatment-naive population. The ERG preferred the 3-knot hazard spline and did not use the JAVELIN part A data in its approach. After technical engagement, the company stated that its approach was taken to supplement the limited data from JAVELIN part B with mature data from JAVELIN part A while maintaining a model based on a treatment-naive population for the earlier part of the curve. The committee noted that both models resulted in similar mean time-on-treatment estimates, and the ICER was not impacted substantially. The clinical experts commented that treatment with avelumab beyond 5 years would be unusual, making the assumptions made about discontinuation of treatment correct. The committee concluded that modelling of time on treatment is appropriate for decision making.

Cost-effectiveness estimate

Avelumab is cost effective compared with chemotherapy

3.10 The company's base-case ICER was £17,947 per quality-adjusted life year (QALY) gained. Using the ERG's preferred propensity score weighting analysis to compare avelumab with chemotherapy (see section 3.5) and the ERG's preferred assumptions for modelling OS, PFS and time on treatment (see sections 3.7 to 3.9), the ICER was £20,780 per QALY gained. These ICERs are either below or within the range normally considered to be an acceptable use of NHS resources (£20,000 to £30,000 per QALY gained). All scenario analyses done by both the company and ERG were also below £25,000 per QALY gained. Therefore, the committee concluded that avelumab is cost effective compared with chemotherapy.

End of Life

Avelumab meets the end-of-life criteria

3.11 In TA517, 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. 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.

Conclusion

Avelumab is a clinically- and cost-effective treatment for metastatic Merkel cell carcinoma

3.12 The committee was reassured that avelumab is an effective treatment for metastatic Merkel cell carcinoma. Updated evidence from JAVELIN and the indirect treatment comparison showed that avelumab improves

overall response rates, PFS and OS compared with chemotherapy. The modelling approaches taken by the company were also considered appropriate. The cost-effectiveness estimates for avelumab are in the range normally considered to be a cost-effective use of NHS resources for life-extending treatments at the end of life. Therefore, the committee recommended avelumab for the treatment of metastatic Merkel cell carcinoma in adults who have not had chemotherapy for metastatic disease.

4 Implementation

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 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 person has metastatic Merkel cell carcinoma 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.

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.

Emily Leckenby
Technical lead

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