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Advising on new medicines for Scotland
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avelumab 20mg/mL concentrate for solution for infusion (Bavencio®)

SMC No 1315/18

Merck Serono Europe Limited/Pfizer

6 April 2018

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

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

avelumab (Bavencio®) is accepted for use within NHS Scotland.

Indication under review: As monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (mMCC).

An uncontrolled phase II study demonstrated that treatment with avelumab for patients with mMCC who had received prior chemotherapy produced improvements in objective response rate, duration of response and overall survival compared with historical chemotherapy controls from a retrospective cohort study

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma.[1]

Dosing Information

10mg/kg body weight administered intravenously over 60 minutes every two weeks.[1]

Treatment should continue until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than two weeks, and no need for salvage therapy, could continue treatment. See the Summary of Product Characteristics (SPC) for further detail.[1]

Treatment should be initiated and supervised by a physician experienced in the treatment of cancer.[1]

Product availability date

October 2017.

Avelumab meets SMC end of life and ultra-orphan criteria.

Orphan designation (EU/3/15/1590) was granted by the European Commission to Merck KGaA, Germany, for recombinant human monoclonal IgG1 antibody (now known as avelumab) against programmed death ligand-1 (PD-L1) for the treatment of Merkel cell carcinoma on 14 December 2015.

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

Background

Avelumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that binds PD-L1 and blocks its interaction with the programmed death 1 (PD-1) and B7-1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic $CD8^+$ T-cells, resulting in the restoration of anti-tumour T-cell responses. Avelumab has also been shown to induce natural killer cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity.[1] Merkel cell carcinoma (MCC) is a very rare cutaneous neuroendocrine tumour and avelumab is the first medicine to be licensed for the treatment of metastatic MCC (mMCC).

Avelumab for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

MCC is a rapidly progressive asymptomatic tumour that readily metastasises and has a high mortality rate. Risk factors associated with MCC are ultra-violet radiation, immunosuppression, integration into tumour DNA of the Merkel cell polyomavirus (a very common virus in the general population), and old age. MCC most often occurs in areas of the skin exposed to the sun such as head and neck (53%) and extremities.[2, 3] A retrospective analysis of patients diagnosed with MCC in Scotland between 2000

and 2010 found a mean age at diagnosis of 78 years.[4] There is currently no clinical consensus on effective treatment. Systemic chemotherapy, (most commonly cisplatin or carboplatin, with or without etoposide) is a treatment option. However, efficacy is short term with median overall survival of 9.6 months from the time of diagnosis of distant metastases and toxicity is a major consideration in the elderly population.[2, 3] There is no evidence that the use of chemotherapy in advanced/metastatic MCC increases progression free survival (PFS) or overall survival (OS).[5] European consensus-based interdisciplinary guidance advises that standard of care should be enrolment in clinical studies. In patients with poor performance status best supportive care (BSC) or palliative radiotherapy should be considered.[3] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely lack of an effective treatment for mMCC. Avelumab meets SMC end of life and ultra orphan criteria.

A patient and clinician engagement (PACE) meeting was held to consider the added value of avelumab in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the rapid and visible disease progression and disfiguring physical manifestations, including fungating, bleeding lesions that are extremely distressing for patients and their families. Participating clinicians also highlighted that, although predominantly a disease of the elderly, it also occurs in younger people.

Impact of new technology

Summary of evidence on comparative efficacy

Evidence supporting the marketing authorisation is from a phase II, single-arm, open-label study, JAVELIN Merkel 200, which was designed in two parts. Part A included patients who had received prior chemotherapy for mMCC and Part B (which is still recruiting) included patients who were chemotherapy-naïve for mMCC.[2, 6 7] The submitting company also presented proxy comparative control data from an in-house retrospective cohort study, 100070-Obs001, of treatment outcomes following chemotherapy in second line and first line treatment cohorts.[2, 8, 9]

JAVELIN Merkel 200 Part A included 88 adults with histologically confirmed stage IV MCC that had progressed after at least one previous line of chemotherapy for metastatic disease. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; estimated life expectancy >12 weeks; ≥1 uni-dimensional measurable lesion by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; and adequate haematological, hepatic and renal function.[6]

All patients received avelumab 10mg/kg by intravenous (IV) infusion over one hour every two weeks until confirmed disease progression, unacceptable toxicity, or other reason for withdrawal. Treatment could continue after progressive disease was observed if there was no significant clinical deterioration (no new symptoms or worsening of existing symptoms), no change in ECOG performance status to ≥3 that lasted more than 14 days, and no investigator assessment that rescue therapy was necessary. Patients with a confirmed complete response were treated for a further six to 12 months (duration decided by the investigator), unless there was a protocol-specified reason for discontinuing treatment. If the investigator considered that treatment beyond 12 months was potentially beneficial, this was permitted.[6]

The primary outcome was the proportion of patients that achieved a confirmed objective (complete or partial) response as the best overall response in the modified intention to treat (mITT) population, defined as all patients who received at least one dose of avelumab. The primary analysis was performed a minimum of six months after the last patient had started study treatment. The primary

outcome was achieved by 32% (28/88) of patients (95% CI: 22.3 to 42.6, Clopper-Pearson). Eight patients had a complete response and 20 had a partial response.[2, 6] Updated analysis at a minimum of 12 months follow up reported similar results: objective response rate (ORR) of 33% (29/88) (95% CI: 23.3 to 43.8, Clopper-Pearson). Ten patients had a complete response and 19 had a partial response.[2]

Secondary outcomes included duration of response, progression free survival (PFS) and overall survival (OS). At the time of the primary analysis 49% (43/88) of patients had died.[6] See Table 1.

Table 1: Secondary outcome results from JAVELIN Merkel 200 Part A (second line therapy in mMCC).[2, 6, 10, 11]

Minimum follow up	**6 months**	**12 months**	**18 months**
Duration of response,* median, months (95% CI)	NR (8.3 to NE)	NR (18.0 to NE)	NR (18.0 to NE)
PFS,* median, months (95% CI)	2.7 (1.4 to 6.9)	2.7 (1.4 to 6.9)	2.7 (1.4 to 6.9)
OS,* median, months (95% CI)	11.3 (7.5 to 14.0)	12.9 (7.5 to NE)	12.6 (7.5 to 19.0)

*Kaplan-Meier estimates; CI=confidence interval; NR=not reached; NE=not estimable; PFS=progression free survival; OS=overall survival

There were no clinically significant changes from baseline in health related quality of life (HRQoL) scores evaluated by the Functional Assessment of Cancer Therapy–Melanoma (FACT-M) and Euroqol 5 dimension (EQ-5D) tools.[2,12] Telephone interviews (concerning prior experience with chemotherapy) were conducted with 19 patients at baseline and (concerning experience with avelumab) with 10 patients at weeks 13 and 25. Only patients with adequately good health at weeks 13 or 25 were interviewed. The investigators noted that patients who withdrew from the study could have had more negative experiences. The conclusions that were reached included: patients reported a clear benefit with avelumab treatment; patient satisfaction with avelumab was high relative to their previous negative experiences with chemotherapy and radiotherapy, which patients described as highly debilitating, both physically and mentally; and that they would recommend avelumab to other patients.[13]

JAVELIN Merkel 200 Part B is an ongoing phase II, single-arm, open-label study of avelumab in patients with mMCC who had not received prior systemic treatment for metastatic disease.[2] Other inclusion criteria were similar to the treatment-experienced Part A study. An interim analysis was performed on 39 patients (from a planned recruitment of 112 patients) who had received at least one dose of avelumab.[7] Interim results are available from 29 of these patients who were followed up for at least 13 weeks. Objective response was achieved in 62% (18/29) (95% CI: 42 to 79) of patients (four patients had a complete response and 14 had a partial response) and this was confirmed by the independent review committee. Median duration of response was not reached (95% CI: 4.0 to not estimable).[2] For the full analysis set (n=39) the Kaplan-Meier estimate of median PFS was 9.1 months (95% CI: 1.9 to not estimable).[2]

Study 100070-Obs001 was a retrospective cohort study of treatment outcomes following chemotherapy and was conducted separately in the US and in Europe.[2, 8, 9] The study had similar eligibility criteria to JAVELIN Merkel 200. It included results from adults diagnosed with stage IV mMCC who were treated between November 2004 and September 2015. Both geographical areas included patients from the second line and first line treatment cohorts and patient-level data were available for analysis.[2]

The cohort of patients who received chemotherapy as second line therapy (n=54) was considered to be a proxy control to JAVELIN Merkel 200 Part A. See Table 2. There were no complete responses and none of the patients maintained a response for more than six months. [2]

The cohort of patients who received chemotherapy as first line therapy was considered to be a proxy control to JAVELIN Merkel 200 Part B. see Table 3. All 67 patients included were from the US. Fifteen per cent (10/67) of patients had a complete response and 16% (11/67) had a partial response.[2]

Table 2: Outcome results for chemotherapy-experienced patients in JAVELIN Merkel 200 Part A and 100070-Obs001 [2, 6, 10, 11]

Outcome	**JAVELIN Merkel 200 Part A (second line avelumab) (n=88)**	**100070-Obs001 (second line chemotherapy)**	
		US (n=20)	**Europe (n=34)**
ORR	32%	20%	8.8%
Duration of response, months (95% CI)	NR (18.0 to NE)	1.7 (0.5 to 3.0)	1.9 (1.3 to 2.1)
PFS, median, months (95% CI)	2.7 (1.4 to 6.9)	2.1 (1.0 to 3.2)	3.0 (2.6 to 3.1)
OS, median, months (95% CI)	12.9 (7.5 to NE)* 12.6 (7.5 to 19.0)**	4.4 (2.2 to 6.2)	5.3 (4.3 to 5.8)

*at minimum 12 months follow up; **at minimum 18 months follow up; ORR = objective response rate; CI=confidence interval; NR=not reached; NE=not estimable; PFS=progression free survival; OS=overall survival

Table 3: Outcome results for chemotherapy-naïve patients in JAVELIN Merkel 200 Part B (interim results) and 100070-Obs001[2, 6, 7, 10, 11]

Outcome	**JAVELIN Merkel 200 Part B (first line avelumab) (n=39)**	**100070-Obs001 (first line chemotherapy) (n=67)**
ORR	62% (n=29)	31%
Duration of response, months (95% CI)	NR (4.0 to NE) (n=29)	5.7 (2.6 to 8.7)
PFS, median, months (95% CI)	9.1 (1.9 to NE)	4.6 (3.0 to 7.0)
OS, median, months (95% CI)	Not reported	10.2 (7.4 to 15.2)

ORR= objective response rate; CI=confidence interval; NR=not reached; NE=not estimable; PFS=progression free survival

A systematic review of chemotherapy outcomes in patients with mMCC was published in 2017. It included 35 studies and identified a range of response rates from 20% to 61%. First line chemotherapy was associated with better response rates (53% to 61%) than second line chemotherapy (23% to 45%). The duration of response across the combined first and second line settings was short (≤8 months).[5]

Summary of evidence on comparative safety

No comparative safety data are available.

Safety data for avelumab are available for patients who had previously received chemotherapy but not for treatment naïve patients. In JAVELIN Merkel 200 Part A, 70% (62/88) of patients had adverse events deemed to be related to avelumab treatment. The most frequent (incidence >10%) were fatigue (24%) and infusion-related reactions (17%). The most severe treatment-related adverse events were grade 3; five events in 4.5% (4/88) of patients: lymphopenia (n=2), increased blood creatine phosphokinase (n=1), increased blood cholesterol (n=1) and increased hepatic aminotransferase (n=1).[6] Treatment-related adverse events that were possibly immune-mediated events were identified in a total of 10 patients.[6]

There were seven treatment-related serious adverse events and these occurred in 5.7% (5/88) of patients: aminotransferase elevation (n=1), infusion-related reaction (n=1), enterocolitis (n=1), chondrocalcinosis and synovitis (both events in one patient), and two events of interstitial nephritis in one patient. Only 2.3% (2/88) of patients permanently discontinued treatment due to treatment-related adverse events (increased aminotransferase and increased creatinine (post-treatment-related acute interstitial nephritis).[6] Dose reduction was required in 9.1% (8/88) of patients and dose delay in 44% (39/88) of patients. In patients assessable for immunogenicity testing 3.8% (3/79) tested positive for treatment-emergent anti-therapeutic antibodies and two of the three immunogenic responses were persistent.[6]

Qualitative information on the relative tolerability of avelumab and prior chemotherapy came from the telephone interviews described above; those concerning prior experience with chemotherapy were conducted with 19 patients at baseline and those concerning experience with avelumab were conducted with 10 patients at weeks 13 and 25. Fatigue with prior chemotherapy was reported by 63% (12/19) of patients; and fatigue with avelumab was reported by 80% (8/10) of patients at week 13, although 50% (5/10) of patients “felt less tired” at week 25. Lack of (or only a very small) negative impact on everyday life with prior chemotherapy was reported by 32% (6/19) of patients and 42% (8/19) of patients reported a substantial negative impact. In contrast, 70% (7/10) patients did not report a negative impact with avelumab; 30% (3/10) reported a need "to rest more often after activities."[14]

Summary of clinical effectiveness issues

Treatment with avelumab in the second line mMCC setting produced improvements in ORR, duration of response and OS, but not PFS, compared with historical chemotherapy controls. The response duration with avelumab in the second line setting (more than 18 months) also compares favourably with results from a systematic review of outcomes of chemotherapy in patients with mMCC that concluded that response duration across the combined first and second line settings was not longer than eight months.[5, 6] Avelumab appears to be fairly well tolerated compared with the known toxicity of chemotherapy, especially in the elderly patient population.[6] There is no robust evidence that avelumab improves quality of life.[2, 13, 14]

The evidence presented for both first and second line treatment settings was a naïve comparison with historical outcomes from a variety of chemotherapy studies within a retrospective cohort study conducted by the submitting company using individual patient level data.

A limitation of the evidence is that it is uncontrolled, although this was accepted by the EMA because recruitment difficulties were anticipated if chemotherapy was to be used as a comparator to avelumab.[2] A total of 14% (12/88) of patients in the JAVELIN Merkel 200 Part A study had at least one important protocol deviation: five patients were enrolled despite being ineligible; five patients took

prohibited medications (steroids used other than to treat immune-related adverse events) and three patients did not receive premedication.

The evidence for avelumab in the first line mMCC setting is weaker as it relies on interim results from approximately a quarter of the planned patient population.[2]

Avelumab has been granted a conditional marketing authorisation from the EMA. The specific obligation to complete post-authorisation measures for the conditional marketing authorisation, is to submit final study results from JAVELIN Merkel 200 Part B by 2020 in order to confirm efficacy for the treatment-naïve patients.

Clinical experts consulted by SMC considered that avelumab is a therapeutic advancement as it is associated with longer responses and less toxicity than chemotherapy and that its place in treatment would reflect its licensed indication, monotherapy in adult patients with mMCC.

At the PACE meeting, the high level of unmet need was highlighted as relapse often occurs during or shortly after chemotherapy, which is devastating for patients and their families. Avelumab treatment was described as being able to transform lives through the opportunity for a longer response duration alongside a more tolerable safety profile. PACE participants reported that the psychological health of both patients and family members noticeably improved following positive responses with avelumab treatment.

Patient and clinician engagement

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of avelumab as an ultra-orphan in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Metastatic MCC is an incurable disease with visible and rapid progression and disfiguring physical manifestations that are extremely distressing for patients and their families. It is more common in the elderly but also occurs in younger people and is associated with underlying immune suppression.
- There is a high level of unmet need as the current treatment is chemotherapy, usually platinum based, and consequently the only option available for frail elderly patients or those with co-morbidities is to receive palliative care. However even those patients who are fit enough to receive chemotherapy usually only have brief tumour responses, with relapses often occurring during or shortly after completion of treatment.
- Avelumab is a novel treatment for metastatic MCC that offers the potential to significantly improve outcomes through longer responses (over 18 months from treatment initiation in some patients). PACE participants described the efficacy benefits in both first and second line treatment, enabling some patients to return to work and other previous activities.
- Avelumab represents an active treatment option for some patients who are not fit enough to receive chemotherapy, due to its more favourable adverse effect profile. Clinicians considered that the risk of immunological adverse effects with avelumab, especially in the initial stages of treatment, was manageable.
- The emotional burden of living with an aggressive and untreatable cancer is exhausting and overwhelming. PACE participants highlighted the importance of the psychological benefits reported by patients receiving avelumab where patients were more optimistic about the opportunity for disease control, a sustained response and being able to tolerate the treatment.

- Avelumab offers the potential to provide large sustained improvements in some patients including the opportunity to shrink visible tumours. Patient groups have reported that the psychological health of family members, as well as patients, noticeably improved following positive responses with avelumab treatment.

Addition of Patient and Carer Involvement

We received a joint patient group submission from the NET Patient Foundation and the Ann Edgar Charitable Trust. The NET Patient Foundation is a registered charity and the Ann Edgar Charitable Trust is a charitable trust. The NET Patient Foundation has received 14% pharmaceutical company funding in the past two years, but not from the submitting company. The Ann Edgar Trust has not received any funding from pharmaceutical companies in the past two years. A representative from the NET Patient Foundation participated in the PACE meeting. The key points of the joint submission have been included in the full PACE statement.

Value for money

The company submitted a cost-utility analysis comparing avelumab to BSC or chemotherapy in treatment naïve (first line) patients and versus BSC in treatment experienced (second line) patients with mMCC. The comparators appear reasonable based on SMC clinical expert feedback.

A three-state partitioned survival model was used, with health states consisting of PFS, post-progression, and death. The time horizon was 40 years, and a weekly cycle length was adopted. PFS and OS estimation for avelumab was based on the single arm JAVELIN Merkel 200 study, which consisted of two patient cohorts. Part A cohort were patients who had failed at least one prior line of chemotherapy (treatment experienced, N=88) and Part B cohort consisted of treatment naïve patients (N=39 currently recruited). PFS and OS outcomes for treatment experienced patients were based on Part A data, and extrapolated using a spline modelling approach in the base case, with conventional parametric functions and mixture cure models applied in scenario analysis. The company argued that spline models are appropriate to handle an expected plateau in PFS and OS outcomes over time, rather than assuming a monotonic PFS/OS risk. For treatment naïve patients the company considered the Part B data to be too immature with insufficient patient numbers to be used for PFS and OS extrapolation. Instead hazard ratios (HR) were assumed for the relationship between treatment naïve versus experienced PFS and OS estimates. For OS this was assumed to be 0.8 in the base case (i.e. better OS in treatment naïve patients) and was validated by expert opinion, and for PFS a HR of one was assumed (mainly as experts were not able to validate a relationship between treatment experienced and naïve patients, and analysis performed by the company using Part A and B data was not felt to produce reliable HR estimates).

For the chemotherapy and BSC comparators, individual patient data from real world observational studies and data from published studies in MCC were used to estimate PFS and OS for treatment experienced and naïve patients, which was extrapolated using parametric functions fitted to the observed data. The efficacy of chemotherapy and BSC was assumed to be the same based on the data available.

Grade 3 or 4 adverse events of greater than 5% incidence for avelumab were drawn from Part A of the JAVELIN Merkel 200 study, and evidence for chemotherapy adverse events were drawn from published evidence in MCC, small cell lung cancer and melanoma. Costs and disutilities for identified adverse events were applied from published sources.

Treatment duration for avelumab in treatment experienced patients was estimated using time on treatment (ToT) data from Part A of the JAVELIN Merkel 200 study. This was extrapolated by fitting

parametric functions to the ToT data, but as the best fitting function resulted in a long tail with a significant proportion of patients projected to stay on treatment for a long duration (>10 years), truncation rules were applied in an attempt to adjust projected ToT to better reflect expected clinical practice. Hence, based on clinical expert opinion it was assumed that a third of patients estimated by the model to be on treatment at 2 years continue (the rest discontinuing) up to a maximum duration of treatment of 5 years at which time point all remaining patients were assumed to have stopped treatment. For treatment naïve patients it was assumed that the ToT assumed for treatment experienced patients would apply for treatment naïve patients (i.e. a HR of one for the treatment naïve versus experienced relationship), with the same 2 and 5 year ToT truncation rules applied.

Utility values for both patient population subgroups were based on regression analysis of EQ-5D-5L data from Part A of the JAVELIN Merkel 200 study. A time to death utility analysis approach was adopted whereby the EQ 5D generated utilities from Part A were applied to time to death states of >100 days, 30-100 days and <30 days, producing estimates of 0.77, 0.75 and 0.71 respectively (with a baseline value of 0.83). The same utility estimates were applied to the treatment naïve economic analysis.

Costs included in the economic analysis were medicine acquisition and administration costs, supportive care costs for on-treatment and off-treatment, radiotherapy costs, adverse event management costs, and end of life costs. Medicine costs estimates for avelumab were based on a methods of moments analysis of Part A data which accounts for the distribution of use of vials by patients, and allows for drug wastage. Chemotherapy costs were based on an assumption of 50% use of carboplatin plus oral etoposide and 50% use of cisplatin plus oral etoposide (a variety of chemotherapies may be used in practice with MCC patients but this was considered a representative regimen to apply) based on clinician feedback, with a maximum duration of 6 cycles of treatment.

The base case results for avelumab, for treatment-experienced patients, was an incremental cost-effectiveness ratio (ICER) of £37,702 per quality adjusted life year (QALY) versus BSC, and for treatment naïve patients the ICERs estimated were £44,218/QALY versus chemotherapy, and £47,200/QALY versus BSC (Table 4). For the treatment naïve analysis the difference in ICERs for the comparison with chemotherapy or BSC was due to the costs applied to the former. The main driver of benefit was associated with life years gained whilst on treatment, and QALYs gained associated with a greater proportion of avelumab patients being in the state of more than 100 days prior to death which is associated with higher health-related quality of life (HRQoL).

Table 4: Base case results (discounted)

Avelumab vs comparator	Incremental cost	Incremental LYs	Incremental QALYs	ICER
Treatment-experienced patients (vs BSC)	£71,266	3.07	1.89	£37,702
Treatment-naive patients (vs chemotherapy)	£67,458	2.67	1.53	£44,218
Treatment-naïve patients (vs BSC)	£71,334	2.67	1.51	£47,200

Sensitivity/scenario analysis demonstrated that the treatment naïve ICERs were sensitive to varying the assumed naïve: experienced HR for the OS and ToT relationship (table 5). In both patient populations there was upward ICER sensitivity to alternative OS extrapolation methods, a shorter time horizon, and alternative scenarios regarding the truncation rules applied for the extrapolation of ToT for avelumab (Table 5).

Table 5: Key sensitivity/scenario analysis results

Sensitivity/Scenario analysis	Treatment naïve ICERs (Avelumab vs BSC)	Treatment naïve ICERs (Avelumab vs chemotherapy)	Treatment experienced (Avelumab vs BSC)
Alternative exploratory utilities for time to death states >100 days (0.70), 30-100 days (0.65), <30 days (0.60)	£52,189/QALY	£48,842/QALY	£41,690/QALY
HR for OS for treatment naïve vs treatment experienced (0.65 – 0.97, log-normal distribution)	£32,692-£77,662/QALY	£30,717 - £72,299/QALY	Not applicable
HR for Time on treatment (ToT) for treatment naïve vs treatment experienced (0.81 – 1.21, log-normal distribution)	£38,088 – £57,736/QALY	£35,191 – 54,655k/QALY	Not applicable
Time horizon 10 years	£70,397/QALY	£65,621/QALY	£47,119/QALY
Time horizon 20 years	£48,421/QALY	£45,354/QALY	£38,610/QALY
Alternative spline models for OS extrapolation:	£46,160 - £65,967/QALY	£43,253 - £61,549/QALY	£36,907 - £45,909/QALY
Alternative parametric functions fitted to the Part A OS data (three best fitting functions: log-log, log-normal, gen gamma)	£50,105 - £75,503/QALY	£46,910 - £70,310/QALY	£39,215 - £49,312/QALY
Mixture cure models for OS extrapolation	£34,441 - £67,543/QALY	£32,349 - £63,019/QALY	£30,491 - £47,331/QALY
50% - 100% of patients continue avelumab at 2 years	£50,135 - £58,938/QALY	£47,125 - £55,846/QALY	£40,049 - £47,087/QALY
Continuation time for 33% of patients (1-3 years)	£39,527 – £52,243/QALY	£36,617 - £49,213/QALY	£31,568 - £41,734/QALY
Discontinuation of avelumab at 3 - 7 years	£43,853 - £49,432/QALY	£40,902 - £46,428/QALY	£35,026 – £39,486/QALY
Removal of ToT truncation rules at 2 and 5 years	£88,538	£85,168	£70,206

There were a number of weaknesses and uncertainties in the economic analyses:

- There are clinical data limitations for avelumab as the estimates of PFS, OS and ToT are based on limited data from a single arm study for treatment experienced patients, and clinical expert opinion used for estimation of these variables for treatment naïve patients rather than the data from the JAVELIN Merkel 200 study. There was uncertainty and ICER sensitivity to OS and ToT extrapolated estimates and the assumptions regarding estimated survival outcomes and avelumab treatment duration for both patient populations, but the ICERs are especially uncertain for the treatment naïve analyses (Table 5).
- In relation to the uncertainties surround the treatment naïve estimates, additional analysis was provided by the company using data from Part B of the JAVELIN Merkel 200 study (treatment naïve patients) for PFS and OS with an adjustment to cap the treatment naïve HR for PFS and OS at no lower than that for treatment experienced patients. This resulted in an ICER of £62,845/QALY vs chemotherapy. Analysis using this approach was not provided for the BSC analysis. This approach may be preferable to the base case analysis and provides some indication of the uncertainty associated with survival estimation in the treatment naïve population.
- The estimated treatment duration with avelumab is uncertain, and based on assumptions regarding the truncation of treatment at 2 and 5 years in both patient populations, with the ICER sensitive to varying these assumptions (Table 5). The truncation also only impacts on reducing incremental costs without consequently impacting on the extrapolated treatment benefits

estimated. A requested exploratory scenario analysis without any truncation rules applied increases the ICERs to £88,538/QALY vs BSC and £85,168/QALY vs chemotherapy in treatment naïve patients and £70,206/QALY vs BSC in treatment experienced patients, although this is based on some patients staying on treatment for a long duration which may not be plausible.

- Assuming the same treatment duration for avelumab in treatment naïve patients as in treatment experienced patients may not be realistic, and could underestimate first line treatment costs. Based on a sensitivity analysis with an upper HR of 1.21 for the ToT relationship between treatment naïve and experienced patients increases the ICERs in the treatment naïve patients to £57,736/QALY vs BSC and £54,655/QALY vs chemotherapy as shown in Table 5.
- The relative treatment effects estimated are based on naïve comparison of avelumab data with data for the comparator from small observational studies, hence are uncertain.
- Utility estimates are based on a time to death analysis based on EQ 5D-5L data, which is a useful approach to assessing the impact of HRQoL decline with cancer progression to death. The estimated utilities from this approach appear high for advanced cancer, which may be related to the utility estimates being based on observations from patients whose disease had not progressed and a limited number of observations in the closer to death states. Requested exploratory scenario analysis applying lower utilities across each time to death state had a modest upward impact on the ICERs across each comparison (Table 5).
- The 40 year time horizon is unnecessarily long, and a more appropriate base case would be 20 to 30 years. Exploring the inherent uncertainty associated with long extrapolation time periods shows the ICERs are sensitive to shortening the time horizon to 10 years (Table 5).

Impact beyond direct health benefits and on specialist services

Avelumab is administered every two weeks, in a day care setting, until disease progression. Compared with cisplatin plus etoposide, treatment with avelumab would require significantly less chair time over the first 18 weeks of treatment. If patients respond well avelumab is likely to be continued for longer than chemotherapy, however the impact on chair time is anticipated to be minimal for the majority of patients.

Avelumab has the potential to provide large sustained improvements in some patients, which may allow family carers, or even patients themselves, to return to work.

Costs to NHS and Personal Social Services

Treatment experienced

The submitting company estimated there would be 1 patient eligible for treatment with avelumab in year 1 rising to 4 patients in year 5. The estimated uptake rate was 100% in year 1 (1 patient) and 100% in year 5 (3 patients) with a discontinuation of 37% applied.

The gross impact on the medicines budget was estimated to be £77k in year 1 rising to £237k in year 5. As no medicines were assumed to be displaced the net medicines budget impact is equivalent to the gross impact.

Treatment-naïve

The submitting company estimated there would be 4 patients eligible for treatment with avelumab in year 1 rising to 12 patients in year 5. The estimated uptake rate was 100% in year 1 (2 patients) and 100% in year 5 (7 patients) with a discontinuation of 37% applied.
The gross impact on the medicines budget was estimated to be £189k in year 1 rising to £623k in year 5. As other drugs are expected to be displaced the net medicines budget impact is expected to be £188k in year 1 rising to £620k in year 5.

The submitting company did not estimate any costs outside the NHS.

Conclusion

The Committee also considered the benefits of avelumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as avelumab is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted avelumab for use in NHS Scotland.

Additional information: guidelines and protocols

Diagnosis and treatment of Merkel Cell Carcinoma; European consensus-based interdisciplinary guideline was published in 2015. It notes that mono- or polychemotherapy can be used in mMCC; however, there is no established standard regimen and responses are usually short-lived. The standard of care is enrolment in clinical studies.[3]

Additional information: comparators

There is no effective treatment for mMCC. Although systemic chemotherapy, most commonly carboplatin or cisplatin plus etoposide has been used to treat mMCC clinical experts have advised SMC that patients with mMCC are now more likely to be treated with an investigative treatment within a clinical study or receive best supportive care. The costs for these chemotherapy regimens are included in the cost table for information.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per 24 weeks (£)
Avelumab	**10mg/kg by IV infusion every two weeks**	**39,936**
Carboplatin* plus etoposide*	Carboplatin target area under the curve 5 (up to 720mg)* by IV infusion on day 1 plus etoposide 80 to 100mg/m^2 IV on days 1 to 3, repeated every 28 days for up to six cycles	Up to 2,274
Cisplatin* plus etoposide*	Cisplatin 60 to 80mg/m^2 IV on day 1 plus etoposide 80 to 120mg/m^2 IV on days 1 to 3 every 21 to 28 days for up to six cycles	751 to 1,073

*I/V=intravenous; *Unlicensed use **Dependent on renal function and body surface area. Cost of avelumab based on 70kg body weight; Doses of carboplatin, cisplatin and etoposide from European Consensus Guideline[3] and based on body surface area 1.8m^2. Doses are for general comparison and do not imply therapeutic equivalence. Cost of avelumab from company submission; costs of carboplatin and etoposide from BNF online and of cisplatin from Dictionary of Medicines and Devices on 11.12.17. Costs calculated using the full cost of vials/ampoules assuming wastage.*

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This assessment is based on data submitted by the applicant company up to and including 6 February 2018.

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

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

Advice context:

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

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