National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Avelumab for treating metastatic Merkel cell carcinoma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Merck Serono	We agree that the populations which form part of the anticipated marketing authorisation should be referred to NICE for evaluation.	Comment noted
Wording	Merck Serono	We consider the wording of the remit of this appraisal to be appropriate.	Comment noted
Timing Issues	Merck Serono	There is a high unmet need in metastatic Merkel cell carcinoma. There are no EMA or MHRA approved treatment options for metastatic MCC patients (mMCC). The only recommended treatment in clinical guidelines is participation in clinical trials (Lebbe 2015). [redacted]	Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
		JAVELIN Merkel 200 data availability JAVELIN Merkel 200 (ClincialTrials.gov identifier: NCT02155647 EudraCT Number: 2014-000445-79) is the pivotal study for avelumab in mMCC. It is designed in two parts to evaluate the efficacy and safety of avelumab in subjects with mMCC (Kaufman 2016d). In Part A (second-line or greater cohort), subjects had received at least one line of chemotherapy for the treatment of mMCC and in cohort B (first-line cohort), subjects are treatment naïve to systemic therapy in the metastatic setting. The study began in July 2014 and is still ongoing. We would like to make NICE aware that recruitment to cohort B only began in 2016 so there will be limited data available in the first line setting by the time of the NICE submission. Further data cuts are planned and will be made available to NICE throughout the appraisal process. For example, [redacted] For Part A, 6 month follow up data was published in 2016 (Kaufman 2016d), including efficacy and safety data for 88 patients. [redacted]	
Additional comments on the draft remit	Merck Serono	None	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Merck Serono	The following points should be included to provide relevant information on the metastatic MCC patient population, making the rarity, prognosis and unmet medical need of this condition clear: • As indicated by its orphan disease designation, MCC is an ultra-rare and aggressive neuroendocrine cutaneous malignancy with poor prognosis (Becker 2010; Lemos 2010). • It is primarily a disease of the elderly, with a median age at diagnosis ranging from 76 to 78 years (Kaae 2010; Kukko 2012; Lemos 2010; Reichgelt 2011). • Fair skin, a history of extensive sun exposure, and photochemotherapy are all associated with an increased risk of MCC - 90% incidence in Caucasians than in other ethnicities (Agelli 2003; Nghiem and Jaimes 2007; Lemos 2010). • MCC has also been associated with autoimmune conditions, immunosuppressive therapy following organ transplantation, and human immunodeficiency virus (HIV) infection, suggesting that impaired immunity is a predisposing factor (Kempf 2013; Engels 2002; Lanoy 2010b; Lanoy 2010a; Lanoy 2009). • Only a few registry studies have reported MCC incidence rates, and these data are variable. o In England, the age-standardised incidence rate of MCC was estimated at 0.2 per 100,000 in 2008 (NCRAS), equating to 106 new cases per year based on a population of 53 million people (NCRAS). o Studies have shown that 35–52% of patients with MCC present with a localised, stage I tumour, 15–26% of patients present with stage II disease, 23–35% with stage III disease, and 5–12% with stage IV. Over 40% of patients presenting with local/ regional tumours subsequently develop recurrent disease (metastatic)	Comments have been noted. The background section is only intended as a briefing document and further detail will be expected in any appraisal submissions. The incidence rate of MCC has been noted in the background section.

Section	Consultee/ Commentator	Comments [sic]	Action
		disease (Allen 2005; Stokes 2009; Andea 2008; Andea 2010; Santamaria-Barria 2013; Fitzgerald 2015). o Based on these figures and assuming similar proportions of patients present with metastatic disease in the UK as in the US, the estimated number of new and recurrent cases of metastatic MCC across the UK per year can be calculated as approximately 40–65 o With the lack of UK epidemiology data, these estimated are based on studies in other countries. We cannot be certain of the exact patient numbers but believe it is highly unlikely to exceed more than 100 patients per year (UK clinician feedback). • Patients with MCC have shorter survival than patients with other aggressive skin malignancies, such as melanoma (Grabowski 2008). o Data from the National Cancer Data Repository (NCDR) in the UK demonstrate high mortality in patients with MCC: between 1999 and 2008, 79% of patients died within 2 years of diagnosis of MCC (NCRAS). • Patients with metastatic MCC have a high unmet need: except in cases with isolated resectable metastases, there are no curative therapies and survival is poor (Voog 1999; Nathan 2016).While there are currently no approved therapies for metastatic MCC, for those who can tolerate it, platinum based chemotherapy has become the standard of care (Aldabagh 2014; NCCN 2016). • Median OS is estimated to be around 9 months in patients with metastatic MCC treated in the first line with chemotherapy (Voog 1999; Nathan 2016, Iyer 2016). In second-line OS ranges from 4.4-5.3 months. Median PFS is only 3 months for first- line treatment and 2 months with second-line treatments (Iyer 2016; Becker 2016; Nathan 2016).	

Section	Consultee/ Commentator	Comments [sic]	Action
		For patients with poor performance status, BSC, which may include palliative radiotherapy can be considered (Lebbe 2015).	
The technology/ intervention	Merck Serono	Please include the following points to ensure the description of the technology is accurate: Avelumab has a proposed dual mechanism of action leveraging the adaptive immune system; binding and blocking the inhibitory signalling through PD-1/PD-L1 resulting in the activation of T-cells and engaging the innate immune system.	Comment noted. We have amended the technology section to reflect comments from the company.
Population	Merck Serono	We believe that the population is accurately defined. There are no subgroups that need to be considered separately.	Comment noted
Comparators	Merck Serono	There are no EMA or MHRA approved treatment options for metastatic MCC patients. The recommended treatment in clinical guidelines is clinical trials (Lebbe 2015). <u>Chemotherapy</u> We agree that chemotherapy is a relevant comparator as it is used in clinical practice for the treatment of mMCC. We understand from clinical expert opinion that there is no standard choice of chemotherapy due to similar clinical efficacy between the different chemotherapy options *Patients with untreated metastatic MCC* In patients with untreated metastatic MCC clinical opinion states that in England and Wales cisplatin ± etoposide phosphate (30%) and carboplatin ± etoposide phosphate (30%) are the most commonly used regimens in the first-line setting. Therefore in the first-line setting a platinum based agent ± etoposide phosphate is the most relevant comparator. Other combinations may be used, including vinka alkyloids and anthracyclines. *Patients with previously treated metastatic MCC*	Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
		In previously treated metastatic MCC the use of chemotherapy is dependent on patient's response in the first line setting. The choice of chemotherapy, if any, depends on the choice and response in first-line. However, chemotherapy may be avoided due to lack of efficacy and patient fitness (UK clinician feedback). Best supportive care We understand from clinical expert opinion that some first-line and second-line patients with mMCC may not be fit enough to receive chemotherapy and their only option in the NHS is best supportive care. Therefore we agree that best supportive care is a relevant comparator in a group of patients who may not be fit enough for chemotherapy.	
Outcomes	Merck Serono	The outcome measures proposed are appropriate. In addition duration (durability) of response should also be included. Unlike chemotherapy where response is short lived, immuno-oncology therapies provide durable responses which is an important indicator of their clinical efficacy.	Comment noted
Economic analysis	Merck Serono	No comment	-
Equality and Diversity	Merck Serono	No comment	-
Other considerations	Merck Serono	No comment	-
Innovation	Merck Serono	Avelumab is a fully human IgG1 monoclonal antibody that inhibits the immune checkpoint protein PD-L-1. It has a proposed dual mechanism of action;	Comment noted. The targeted mechanism of action has been

Section	Consultee/ Commentator	Comments [sic]	Action
		binding and blocking the inhibitory signalling through PD-1 resulting in the activation of T-cells and engaging the innate immune system Avelumab is a step change therapy in the treatment of metastatic MCC where disease progression is aggressive, prognosis is poor and there are no approved therapies. Avelumab has been granted Orphan Drug, Fast Track, and Breakthrough Therapy designations by the FDA, and Orphan Drug designation by the EMA based on preliminary evaluation of data from the Phase II JAVELIN Merkel 200 study. FDA Priority Review is currently underway. There is a strong rationale for targeting PD-1/PD-L1 in MCC. JAVELIN Merkel 200, the largest trial in mMCC to date, is a Phase II trial assessing the efficacy and safety of avelumab in patients with chemorefractory mMCC; the study has recently been expanded to previously untreated patients with mMCC who are treated with avelumab in the first line. The initial results of the trial show clear clinical activity of avelumab in patients with previously treated disease; 32% of patients achieved an objective response to treatment, with 8 patients achieving a complete response, a further 10% of patients had stable disease. Responses to avelumab were durable: most responses (92%) were sustained for at least 6 months, and 82% of patients were still in response after a median of 10.4 months of follow-up. Subgroup analyses suggested a higher response rate in patients receiving avelumab as a second-line treatment for mMCC (ORR 38.4%) compared with a third-line or later treatment (ORR 19.4%). DoR already exceeds that reported with chemotherapy in mMCC in both the first- and second-line treatment settings (Iyer 2016). Furthermore, 6-month PFS rate was 40% and 6-month OS rate was 69% (Kaufman 2016d). Responses to avelumab were observed irrespective of PD-L1 expression or MCPyV status, indicating benefit for all patients with mMCC. Avelumab has demonstrated a manageable safety profile, not only in the JAVELIN Merkel 200 (Kaufman 2016), but also in the JAVELIN Solid Tumor study, that was a broad phase Ib study investigating avelumab across a	included in the technology section of the scope. In the appraisal submission the company can provided further details on the innovative nature of the technology.

Section	Consultee/ Commentator	Comments [sic]	Action
		number of tumours, currently safety data in 1300 patients has been reported, with treatment-related AEs were reported in 62.5% of patients and were mostly grade 1 or 2. The most common treatment-related AEs were fatigue, infusion-related reactions, nausea, chills, diarrhoea and pyrexia. Treatment-related grade ≥3 AE were reported in <10% of patients; the most common were gamma-glutamyl transferase elevation, infusion-related reaction, fatigue, lipase elevation, anaemia and dyspnoea (Kelly 2016). Avelumab has demonstrated a favourable tolerability profile consistent with that seen with other anti-PD-1/PD-L1 therapies, and contrasts strongly with the high rate of SAEs and toxic death associated with chemotherapy in patients with mMCC (Voog 1999). A positive association was observed between clinical response to avelumab (% reduction in tumour size) and subjects' health-related quality of life. Together, these data support avelumab as an innovative new therapeutic option for patients with metastatic MCC.	
Questions for consultation	Merck Serono	**Where do you consider avelumab will fit into the existing skin cancer NICE pathway?** As a treatment option for people with metastatic Merkel cell carcinoma. Under the existing NICE skin cancer pathways, the treatment of MCC with avelumab could sit within a new pathway for merkel cell carcinomas. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims.** We believe that the proposed remit meets the commitment to promoting equality of opportunity.	Comment has been noted. Comment has been noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	NCRI-ACP-RCP-RCR	**Q1 Which treatments are considered to be established clinical practice in the NHS for untreated metastatic Merkel carcinoma?** • **Which treatments is avelumab expect to replace for untreated metastatic Merkel carcinoma?** There is no established treatment in untreated metastatic MCC. Commonly used chemotherapy include single and dual agent treatment with Cisplatin, carboplatin, etoposide and topotecan. The small number of patients diagnosed with this condition limits clinical trials hence there are no established guidelines or single standard practice. Chemotherapy response rate is usually in the range of 60% partial responders with relapse usually within 3 months. Response to chemotherapy is therefore not durable. In view of the recently published JAVELIN trial data, avelumab has potential to replace chemotherapy as first line treatment in metastatic untreated MCC. **Q2 Which treatments are considered to be established clinical practice in the NHS for previously metastatic Merkel carcinoma?** • **Which treatments is avelumab expect to replace for previously metastatic Merkel carcinoma?** There is no treatment established as second line in metastatic MCC. Some limited data suggest pazopanib, sandostatin or imatinib (or combination) may be useful. Very limited numbers of patients hence limited data and as with first line, no established guidelines or practice exists. Based on the JAVELIN trial data, avelumab has the potential for being second line treatment in metastatic chemorefractory MCC. **Q3 Are the outcomes listed appropriate?** Yes	Comment has been noted. Chemotherapy and best supportive care are the comparators defined in the scope. Comment has been noted. Comment has been noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		Q4 Are there any subgroups of people in whom avelumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Due to the very small number of patients it is not possible to separate any group with metastatic MCC that could benefit more from this treatment. **Q5 Where do you consider avelumab will fit into the existing skin cancer NICE pathway?** There is no standard NICE pathway for MCC currently. This guidance would set the national standard of care	Comment has been noted. Comment has been noted
Additional comments on the draft scope	Merck Serono	Absence of the following consultee and commentators: • Rare Disease UK • Genetic Alliance • NET Patient Foundation • UK and Ireland Neuroendocrine Tumour Society (UKI NETS) • Specialised healthcare alliance (SHCA) • The International Alliance Against Cancers of the skin	Comment noted. We have amended the matrix to include the relevant identified organisations.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Association of Dermatologists

Department of Health