Indication	For the treatment of previously untreated metastatic Merkel cell carcinoma. For the treatment of previously treated (with systemic cytotoxic chemotherapy) metastatic Merkel cell carcinoma
Treatment Intent	Palliative
Frequency and number of cycles	Every 2 weeks (14 days) Until disease progression or unacceptable toxicity or patient choice. A formal medical review as to whether treatment with avelumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
Monitoring parameters pre-treatment	• Thyroid function and 9am cortisol level must be assessed at baseline then every 6-8 weeks. • Monitor FBC, LFT, U&E, glucose at each cycle • If the patient has brain metastases, then the patient should have been treated for these and be symptomatically stable prior to starting avelumab. • **Renal impairment:** No dose adjustment in mild or moderate renal impairment (30-89ml/min). There are insufficient data in patients with severe renal impairment (<30ml/min) for dosing recommendations. • **Hepatic impairment:** No dose adjustment is needed for patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 × to 1.5 × ULN and any AST). There are insufficient data in patients with moderate or severe hepatic impairment (bilirubin >1.5 x ULN) for dosing recommendations. • **Infusion-related reactions:** see table 1. Monitor for pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. In case of recurrence of Grade 1 or Grade 2 infusion-related reaction, the patient may continue to receive avelumab under close monitoring, after appropriate infusion rate modification and premedication with paracetamol and antihistamine. • **Management of adverse reactions and dose adjustments**: Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability; see Table 1. For Immune-related adverse reactions, based on the severity of the adverse reaction, avelumab should be withheld and corticosteroids administered. If corticosteroids are used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. • **Concomitant medication / Drug interactions**: No interaction studies have been conducted with avelumab. • Each patient should be given an immunotherapy alert card (to be carried until at least 5 months after the last dose of treatment) and patients must be advised to contact the oncology team or the 24 hour hot-line immediately they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment. • The use of systemic corticosteroids or immunosuppresants before starting avelumab should be avoided. • Avelumab can cause fatigue in some patients and therefore use caution when driving or using machines.
Reference(s)	Avelumab SPC accessed online 24/06/20 CDF list v1.165 accessed online 24/06/20 KMCC protocol SKI-011 v1

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Guidelines for withholding or discontinuation of Avelumab

Treatment-related adverse reaction	**Severity***	**Treatment modification**
Infusion-related reactions	Grade 1 infusion-related reaction	Reduce infusion rate by 50%
	Grade 2 infusion-related reaction	Withhold until adverse reactions recover to Grade 0-1; restart infusion with a 50% slower rate
	Grade 3 or Grade 4 infusion-related reaction	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold until adverse reactions recover to Grade 0-1
	Grade 3 or Grade 4 pneumonitis or recurrent Grade 2 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN	Withhold until adverse reactions recover to Grade 0-1
	AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN	Permanently discontinue
Colitis	Grade 2 or Grade 3 colitis or diarrhoea	Withhold until adverse reactions recover to Grade 0-1
	Grade 4 colitis or diarrhoea or recurrent Grade 3 colitis	Permanently discontinue
Pancreatitis	Suspected pancreatitis	Withhold
	Confirmed pancreatitis	Permanently discontinue
Myocarditis	Suspected myocarditis	Withhold
	Confirmed myocarditis	Permanently discontinue
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycaemia)	Grade 3 or Grade 4 endocrinopathies	Withhold until adverse reactions recover to Grade 0-1
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times ULN	Withhold until adverse reactions recover to Grade 0-1
	Serum creatinine more than 6 times ULN	Permanently discontinue
Other immune-related adverse reactions (including myocarditis myositis, hypopituitarism, uveitis, Guillain-Barré syndrome)	For any of the following: • Grade 2 or Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above.	Withhold until adverse reactions recover to Grade 0-1
	For any of the following: • Life threatening or Grade 4 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy) • Recurrent Grade 3 immune-related adverse reaction • Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks • Persistent Grade 2 or Grade 3 immune-mediated adverse reactions lasting 12 weeks or longer	Permanently discontinue

Repeat every 2 weeks (14 days)

Day	Drug	Dose	Route	Infusion Duration	Administration Details
1	Paracetamol	1g	PO	STAT	Given at least 30 minutes before the Avelumab infusion. May be omitted if the first four infusions are completed without an infusion-related reaction.
	Chlorphenamine	4mg	PO	STAT	
	Avelumab	**800mg**	IVI	60 Minutes	In 250ml 0.9% Sodium chloride via low-protein binding in-line or add on 0.2 micrometre filter Flush line with sodium chloride 0.9%

TTO	Drug	Dose	Route	Directions
	Metoclopramide	10mg	po	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2-4mg	po	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.