Systemic Anti Cancer Treatment Protocol

Avelumab
Merkel Cell Carcinoma

PROTOCOL REF: MPHAAVELSK
(Version No: 1.1)

Avelumab is a human monoclonal IgG1 antibody directed against the immunomodulatory cell surface ligand protein PD-L1 and is produced in Chinese hamster ovary cells by recombinant DNA technology.

The PD-1 pathway represents a major immune control switch which may be engaged by tumour cells to overcome active T-cell immune surveillance.

Approved for use in:

Previously untreated (with systemic therapy) metastatic Merkel call carcinoma, when certain criteria are met, via the **Cancer Drugs Fund** initially then NICE approved.
Previously treated (with systemic cytotoxic chemotherapy) metastatic Merkel cell carcinoma, when certain criteria are met, via **Cancer Drugs Fund** initially then NICE approved.

Blueteq registration is required.

Exclusions:

Performance status of 2 or more.
Brain metastases that are not treated and are not stable.
Any other concomitant SACT treatment.
History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, active hepatitis B or C infection.
Active infection requiring systemic treatment.
History of clinically severe autoimmune disease.

Dosage:

Drug	Dosage	Route	Frequency
Avelumab	800mg	IV infusion	2 weekly

Repeated every 2 weeks until loss of clinical benefit or unacceptable toxicity occurs. Dose reductions and escalations are not recommended.

Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms **and** no change in performance status for greater than two weeks, **and** no need for salvage therapy, could continue treatment. (All 3 conditions must apply).

Supportive therapy:

Patients should be pre-medicated with chlorphenamine 10mg IV and paracetamol 1g Po prior to the first 4 infusions of avelumab. If the fourth infusion is completed without an infusion-related reaction, premedication for subsequent doses should be administered at the discretion of the physician.

Extravasation risk:

Monoclonal antibody – treat symptomatically, no specific recommendations.

Administration:

Day	Drug	Dose	Route	Diluent and rate
1	Chlorphenamine	10mg	IV	30 minutes prior to avelumab
1	Paracetamol	1000mg	Oral	30 minutes prior to avelumab
1	Avelumab	800mg	IV infusion	250mL sodium chloride 0.9%. Infused over 60 minutes in a non-pyrogenic line with a 0.2 micron filter

Main Toxicities:

Immune-Mediated Pneumonitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management: https://www.clatterbridgecc.nhs.uk/professionals/guidance-1
Immune-Mediated Colitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other Immune-Mediated Toxicities: Hepatitis, adrenal insufficiency, type 1 diabetes mellitus, nephritis, hyperthyroidism or hypothyroidism Less frequently (reported in less than 1% of patients): Myocarditis, myositis, hypopituitarism, uveitis and Guillain-Barr é syndrome.	Monitor LFTs, biochemistry, bloody glucose, cortisol, creatinine and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management: https://www.clatterbridgecc.nhs.uk/professionals/guidance-1
Other non-immune adverse events: Fatigue, nausea, diarrhoea, decreased appetite, constipation, infusion related reactions, weight loss, vomiting, dyspnoea, abdominal pain, anaemia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management: https://www.clatterbridgecc.nhs.uk/professionals/guidance-1
Common laboratory abnormalities: Gamma-glutamyltransferase increased, blood alkaline phosphatase increased, amylase increased, lipase increased, blood creatinine increased	Refer to Immuno-Oncology toxicity specific guidance for adverse event management: https://www.clatterbridgecc.nhs.uk/professionals/guidance-1
Infusion related reactions	Grade 1 to 2: stop the infusion, administer antihistamine and corticosteroids as required, when recovered continue with reduction of infusion to 50% of initial rate Grade 3 / 4: discontinue permanently

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Home treatment if eligible	Cycle 3	Prior to cycle 5	Ongoing
Informed Consent	X						
Clinical Assessment	X					X*	Every 12 weeks thereafter or as clinically indicated
SACT Assessment (to include PS and toxicities)	X	X	X		X		Every cycle
FBC, U&E, Magnesium, LFTs, LDH	X	X	X		X		Every cycle
TFTs, cortisol, blood glucose, lipid profile (cholesterol)	X						Every 6 weeks/if clinically indicated
CrCl (Cockcroft and Gault)	X						Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal
CT scan	X						Every 6 months/if clinically indicated
Trop-T, CK, pro-BNP	X						At baseline then if clinically indicated
ECG							If clinically indicated
Blood pressure measurement	X	X	X		X		Every cycle
Respiratory Rate							If clinically indicated
Weight recorded	X	X	X		X		Every cycle
Height recorded	X						

*Formal medical review (can be virtual) to assess the tolerability of treatment and whether treatment should continue (as per NHS England criteria).

Pregnancy test if applicable
Serum samples for HIV, Hep C antibody & HBsAg if risk factors.

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 of cycle if:-

Hb > 9g/L	ANC ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

Confirm any deferrals with the prescribing oncologist.

Non-haematological toxicity

Toxicity Grade	Action
Grade 1	No action. Provide symptomatic treatment
Grade 2	Withhold avelumab until resolved to <grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management. https://www.clatterbridgecc.nhs.uk/professionals/guidance-1
Grade 3 and Grade 4	Discontinue avelumab. Refer to Immuno-Oncology toxicity specific guidance for adverse event management: https://www.clatterbridgecc.nhs.uk/professionals/guidance-1 Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisolone equivalent within 12 weeks of toxicity.

Avelumab will be permanently discontinued for any Grade 3-4, severe or life-threatening adverse reaction.

Hepatic Impairment

No studies have been conducted on patients with moderate or severe hepatic impairment.

No dose adjustments are required for mild hepatic impairment.

Renal Impairment

No studies have been conducted on patients with severe renal impairment.

No dose adjustments are required for mild to moderate renal impairment.

Patient Counselling Points

Contact the triage team for the following:

New or worsening cough, chest pain or shortness of breath

Diarrhoea or severe abdominal pain

Jaundice, severe nausea or vomiting, or easy bruising or bleeding

Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes

Monitor for signs of infection / sepsis

References:

SmPC from Merck – Pfizer 03 Jan 2018

National Cancer Drugs Fund List ver1.67 01-Mar-18