SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Avelumab
Urothelial Carcinoma and Merkel Cell Carcinoma

PROTOCOL REF: MPHAAUCM
Version No.: 1.0

Approved for use in:

Urothelial Carcinoma

Monotherapy for the **MAINTENANCE treatment** of adult patients with **locally advanced or metastatic urothelial carcinoma who have just completed and not progressed on FIRST line platinum-containing combination chemotherapy** satisfies the following criteria:

- Received at least 4 cycles (and no more than 6) of gemcitabine in combination with cisplatin or carboplatin.
- Radiological evidence of complete response, partial response or stable disease on completion of chemotherapy.
- ECOG performance status score of 0 or 1.

Merkle Cell Carcinoma

Monotherapy as **FIRST line treatment for metastatic Merkel cell carcinoma**.
ECOG performance status score of 0 or 1.

Monotherapy as **SECOND line treatment for metastatic Merkel cell carcinoma** and fulfills the following criteria:

- Previously treated with 1 or more lines of cytotoxic chemotherapy but has **NOT RECEIVED** any prior treatment with any anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4] antibody.
- ECOG performance status score of 0 or 1

******Blueteq registration REQUIRED for ALL INDICATIONS******

Exclusions

- History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, myocarditis, active hepatitis B or C infection
- Active infection requiring systemic treatment
- Less than 4 weeks from major surgery
- History of clinically severe autoimmune disease

Dosage:

Drug	Dose	Route	Frequency
Avelumab	**800mg**	IV infusion	**2 weekly**

Urothelial carcinoma- treatment to continue until disease progression or unacceptable toxicity or after a maximum of 5 calendar years of avelumab treatment (whichever of these events occurs first).

Merkel cell carcinoma- treatment to continue until disease progression or unacceptable toxicity. **NOTE:** 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 2 weeks and no need for salvage therapy: all 3 conditions must apply) can continue treatment.

Extravasation risk

Avelumab (monoclonal antibody): NON-VESICANT

Refer to Clatterbridge 'Prevention and Management of Extravasation Injuries' Policy for further guidance.

Dosing in renal and hepatic impairment (Prior to start of treatment ONLY/Baseline):

Renal	GFR ≥ 30ml/min- proceed with treatment. GFR < 30ml/min- limited data, proceed with caution.

Hepatic	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 × ULN and any AST) or Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. * Within normal limits or high

Patient Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 1 month following the last dose of avelumab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- 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

Interactions:

Avelumab is primarily metabolised through catabolic pathways, therefore, it is not expected that avelumab will have pharmacokinetic drug-drug interactions with other medicinal products.

For more detailed interactions please refer to the SPC.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Chlorphenamine***	**10mg**	**IV**	30 minutes before Avelumab
	Paracetamol*	**1000mg**	**IV/PO**	30 minutes before Avelumab Administer IV for the first TWO cycles. If no IRR switch to oral route from cycle 3 onwards.
	Avelumab in 250mls of sodium chloride 0.9% solution	800mg	**IV**	**Over 60 minutes** using a sterile, non-pyrogenic, low-protein binding 0.2 micrometer in-line or add-on filter

*PRE-MEDICATION with an antihistamine and with paracetamol is REQUIRED prior to the first FOUR infusions of avelumab. If the fourth infusion is completed without an infusion-related reaction (IRR), premedication for subsequent doses should be administered at the discretion of the physician. **Patients should be monitored for signs and symptoms including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. Refer to 'Dose modification and toxicity management' section for details on management of IRRs.**

Main toxicities:

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Frequency and/or Grade	Toxicity
Immune-related	Pneumonitis Hepatitis Colitis Pancreatitis Myocarditis Endocrinopathies- thyroid disorders, adrenal insufficiency, typer 1 diabetes mellitus

	Nephritis and renal dysfunction Others (< 1% of patients)- myositis, hypopituitarism, uveitis, myasthenia gravis, myasthenic syndrome, cystitis noninfective, and Guillain-Barré syndrome
Most common- any grade	Fatigue (30.0%) Nausea (23.6%) Diarrhoea (18.5%) Constipation (18.1%) Decreased appetite (17.6%) IRR (15.9%) Vomiting (15.6%) Weight decreased (14.5%)
Most common- grade ≥ 3 Serious adverse reactions were immune-related adverse reactions and IRR	Anaemia (5.6%) Hypertension (3.9%) Hyponatraemia (3.6%) Dyspnoea (3.5%) Abdominal pain (2.6%).

Investigations and treatment plan:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x		x	x	For the first three cycles then every three months or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (ALT, AST and Bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x	x	Every cycle
Lipid profile (cholesterol)	x				At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x				At baseline then if clinically indicated
Creatinine Clearance (Cockcroft and Gault)	x				Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
CT scan	x				Every 12 weeks or as clinically indicated
ECG	x				**At baseline** (refer to 'Pre-assessment Baseline Cardiac Pathway' guidance) **for all Renal and Melanoma and thereafter as clinically indicated** (ECG to be reviewed by clinical team)
Trop-T, CK, pro-BNP	x				

Full set of observations (*BP, heart rate, temperature, respiratory rate and O2 sats)*	x	x	x	x	Every cycle
Weight recorded	x	x	x	x	Every cycle
Height recorded	x				

Dose modification and toxicity management:

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of doses are contained in dose modifications.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Treatment Threshold

Administer treatment on day 1 if:

Platelets	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤ 1.5 ULN or baseline	<3 x ULN	<5 x ULN	<5 x ULN	Within range or no change from base line

ULN = upper limit of normal

Platelets must be within normal range prior to Cycle 1.

Toxicity management:

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Infusion-related reactions (IRR)

Grade	Action
1	Slow the infusion rate by 50% for the remainder of the infusion If grade 1 IRR recurs, reduce infusion rate by 50% and pre-medicate with IV chlorphenamine and paracetamol prior to all subsequent avelumab infusions.
2	Withhold infusion until Grade 1 or resolved, restart infusion at a 50% slower rate. If grade 2 IRR recurs, reduce infusion rate by 50% and pre-medicate with IV chlorphenamine and paracetamol prior to all subsequent avelumab infusions.
3 or 4	the infusion should be stopped and avelumab should be permanently discontinued

Other toxicities

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4	Withhold treatment.

Severe	Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

References:

1. Bavencio 20mg/ml solution for infusion SmPC. Merck-Pfizer (Last updated 27th May 2022)

2. Krens S D, et al (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*; 20: e201–08.

3. Powles T, et al (2020). Avelumab Therapy for Advanced or Metastatic Urothelial Carcinoma. *NEJM*. 24; 383(13): 1218-1230.

4. NICE TA788: Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy. Published: 11 May 2022.

5. NICE TA691: Avelumab for untreated metastatic Merkel cell carcinoma. Published: 21 April 2021.

6. NICE TA517: Avelumab for treating metastatic Merkel cell carcinoma. Last updated: 21 April 2021.

Circulation/Dissemination

Date added into Q-Pulse	28th April 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
February 2023	1.0	**Hala Ghoz** **Protocols Pharmacist**	**Combined UC and Merkel Cell protocols**