Indication	For unresectable locally advanced or metastatic renal cell carcinoma (RCC). Patients should be treatment-naïve, or if the patient has received prior systemic therapy in the context of adjuvant/neoadjuvant therapy, then such treatment was completed >/=12 months previously.
Treatment Intent	Palliative
Frequency and number of cycles	Every 28 days Continue until disease progression or unmanageable toxicity or patient choice. A formal medical review must be scheduled to occur by the start of the 3rd cycle of treatment to assess tolerance and regular reviews should continue thereafter.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Thyroid function must be assessed at baseline then every 8 weeks or as clinically indicated. • Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose. • Monitor FBC, LFT, U&E, glucose on day 1 and 15 of each cycle. If haemoglobin or haematocrit are elevated above the normal level d/w consultant. • Proceed with the next dose of avelumab if: Platelets >/=75 x 10^9 /l and Neutrophils >/=1.0 x 10^9 /l and AST/ALT</= 3 x ULN and Bilirubin </=1.5 x ULN and Serum creatinine </= 1.5 x baseline and TSH / free T4 within range, or no change from baseline. • Dipstick urine for proteinuria at each cycle. Report to consultant if protein >/= 2+ (or >/= 1g/24hr) • BP baseline and on day 1 and 15 of each cycle. Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension, despite use of anti-hypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. • The patient should have no symptomatically active brain metastases or leptomeningeal metastases currently requiring steroids for symptom control. • ECG at first cycle and as clinically indicated. Monitor for signs and symptoms of cardiac failure during treatment. • **Hepatic Impairment:** o Avelumab: 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. o Axitinib: No dose reduction required in mild hepatic impairment. A dose decrease is recommended in moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Not to be used in severe hepatic impairment (Child-Pugh class C). • **Renal Impairment:** o Avelumab: 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. o Axitinib: No dose reduction required in renal impairment if CrCl >/= 15ml/min. • Axitinib should be used with caution in patients at risk of or with a history of embolic and thrombolic events.

- The use of systemic corticosteroids or immunosuppressants before starting avelumab should be avoided.
- **Infusion-related reactions:** Monitor for pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria.
  For Grade 3 or Grade 4 infusion-related reactions, the infusion should be stopped and avelumab should be permanently discontinued. For Grade 1 infusion-related reactions, the infusion rate should be slowed by 50% for the current infusion. For patients with Grade 2 infusion-related reactions, the infusion should be temporary discontinued until Grade 1 or resolved, then the infusion will restart with a 50% slower infusion rate.
  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.
- **Dose modification and management of adverse reactions:**
  - **Avelumab:** 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 (e.g pneumonitis, hepatitis, colitis, pancreatitis, myocarditis), 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.
  - See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/
  - **Axitinib:** If a patient tolerates the starting dose of 5 mg twice daily with no adverse reactions > Grade 2 for two consecutive weeks the dose can be increased to 7 mg twice daily unless the patient's blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment. Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7 mg twice daily may have their dose increased to a maximum of 10 mg twice daily.
  - Dose reduction of Axitinib: first dose reduction to 3mg twice daily and second dose reduction 2mg twice daily. No further dose reduction recommended.
  - Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving axitinib, in patients with signs or symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment.
- Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.
- Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery.
- For patients who develop moderate to severe proteinuria (>/=2+ on dipstick, or >/=1g/24 hours), reduce the dose or temporarily interrupt axitinib.
- If either avelumab or axitinib has to be permanently discontinued on account of toxicity, treatment with the other drug can be continued as monotherapy as long as there is no evidence of progressive disease.
- **Common drug interactions (for comprehensive list refer to BNF/SPC):**
- No interaction studies have been conducted with avelumab.
- Avoid concomitant treatment of potent CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin) or inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine) with axitinib. If a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose is recommended. If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered. If a strong CYP3A4/5 inducer must be co-administered, a gradual dose increase of axitinib is recommended. If the dose of axitinib is increased, the patient should be monitored

	carefully for toxicity. If co-administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer. • 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. • Patients should be given the Bavencio® patient alert card and the patient safety leaflet "Important safety information to minimise the risk of immune-related side effects" • Driving: Avelumab and Axitinib can cause fatigue in some patients and therefore use caution when driving or using machines. • Axitinib for oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	CDF list v1.255 accessed online 23.03.2023 KMCC protocol RCC-011 V1 SPC accessed online 22.09.2023

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**
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 (axitinib and avelumab)	If ALT or AST ≥ 3 times ULN but < 5 times ULN or total bilirubin ≥ 1.5 times ULN but < 3 times ULN.	Withhold avelumab and axitinib until these adverse reactions recover to Grades 0-1. If persistent (greater than 5 days), consider corticosteroid, prednisolone or equivalent followed by a taper. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. Dose reduce axitinib as per dose modification guidelines.
	If ALT or AST ≥ 5 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN or total bilirubin ≥ 3 times ULN	Permanently discontinue both avelumab and axitinib and consider corticosteroid therapy.
Hepatitis (avelumab only)	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
Skin reactions	Grade 3 rash	Withhold until adverse reactions recover to Grade 0-1
	Grade 4 or recurrent Grade 3 rash or confirmed Stevens–Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)	Permanently discontinue
Other immune-related adverse reactions (including-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 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1 and 15	Paracetamol	1gm	PO	STAT	Given at least 30 minutes before the Avelumab infusion.
	Chlorphenamine	10mg	IV	STAT	May be omitted if the first four infusions are completed without an infusion-related reaction.
	AVELUMAB	**800mg**	IV	60min	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	
Day 1	**AXITINIB**	**5mg**	PO	BD (12 hours apart) continuously. Swallow this medicine whole with a glass of water with or without food. Do not chew or crush. Do not take with grapefruit or grapefruit juice. Available as 1mg, 3mg, 5mg and 7mg tablets.	
	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. Do not take for longer than 3 days without contacting the oncology team. Dispense 30 capsules on cycle 1 then only if required.	