Systemic Anti Cancer Therapy Protocol

Avelumab in Combination with Axitinib Advanced Renal Cell Carcinoma

PROTOCOL REF: MPHAAAAUR
(Version No: 1.0)

This protocol has been temporarily amended - please see the SRG Guidelines during COVID-19 Urology Cancer.

Approved for use in:

First line treatment for adult patients with advanced renal cell carcinoma which has either a clear cell component or is one of the types of RCC outlined in blueteq the form.

ECOG performance status 0 or 1.

Blueteq registration required: check Blueteq for full eligibility criteria

Dosage:

Drug	Dose	Route	Frequency
Avelumab	**800mg**	IV infusion	Days 1 and 15
Axitinib	**5mg twice daily**	Oral	Every 28 days

Every 28 days until disease progression or unacceptable toxicity

Administration:

Take axitinib with or without food approximately 12 hours apart, swallow whole with a glass of water.

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

Domperidone- 10mg three times a day if required

Extravasation risk:

Avelumab (monoclonal antibody) - neutral.

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

Dosing in renal and hepatic impairment:

Renal	Avelumab	GFR ≥ 30 ml/min: no dose adjustment is needed GFR <30 ml/min and patients on haemodialysis: no need for dose adjustment is expected. **Use with caution as not tested in this patient cohort**
	Axitinib	Renal impairment: no dose adjustment is needed Haemodialysis no need for dose adjustment is expected

Hepatic	Avelumab	Mild**:** Bil >1.0-1.5 x ULN and any AST or Bil ≤ULN and AST >ULN no dose adjustment is needed Moderate: Bil 1.5-3 x ULN, with any AST or severe Bil >3.0-10 x ULN, with any AST no need for dose adjustment is expected. Use with caution as not tested in this patient cohort
	Axitinib	Mild hepatic impairment (Child-Pugh class A)- No dose adjustment Moderate hepatic impairment (Child-Pugh class B)- recommend reduce starting dose from 5 mg twice daily to 2 mg twice daily. Severe hepatic impairment (Child-Pugh class C) - not studied in this group of patients, not recommended.

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.

Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, **phenobarbital** and **St. John's wort**) may decrease axitinib plasma concentrations.

For more detailed interactions please refer to the SmPC.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Chlorphenamine**	**10mg**	**IV**	30 mins before Avelumab
	Paracetamol	**1000mg**	**PO**	30 mins before Avelumab
	Avelumab* in 250mls of sodium chloride 0.9% solution	800mg	**IV**	**Over 60 minutes** using a sterile, non-pyrogenic, low-protein binding 0.2 micrometre in-line or add-on filter
	Axitinib	**5mg twice daily**	**PO**	28 day supply
15	**Chlorphenamine**	**10mg**	**IV**	30 mins before Avelumab
	Paracetamol	**1000mg**	**PO**	30 mins before Avelumab
	Avelumab* in 250mls of sodium chloride 0.9% solution	800mg	**IV**	**Over 60 minutes** using a sterile, non-pyrogenic, low-protein binding 0.2 micrometre filter

*Patients have to be pre-medicated with an antihistamine and with paracetamol 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. Please refer to the CCC Hypersensitivity; Management Prevention Policy

Main toxicities:

Loose stools, nausea, constipation, vomiting, hypertension, fatigue, hoarse voice, weight loss, underactive thyroid gland, joint pain, back pain, belly pain, skin rash, itching. For further toxicities please refer to the SPC for avelumab and axitinib.

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 1 day 15	Cycle 2	Cycle 2 day 15	Cycle 3	Cycle 3 day 15	Ongoing
Informed Consent	X							
Clinical Assessment	X			X		X		For the first three cycles then every three months
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every review
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs, TFTs, cortisol, blood glucose	X	X	X	X	X	X	X	Every cycle
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
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 12 weeks
Trop-T, CK, pro-BNP	X							As clinically indicated ***At baseline for all Renal and Melanoma** (ECG to be reviewed by clinical team)
ECG	X							
Urine protein dipstick								If clinically indicated
Blood pressure measurement	X			X		X	X	Every review

Weight recorded	X	X	X	X	X	X	X	Every review
Height recorded	X							
Lipid profile	X					X		Every 6 weeks
Full set of observations (BP, hear rate, temperature, respiratory rate and O2 sats)	X	X	X	X	X	X	X	Repeat if clinically indicated every 6 weeks

Dose Modifications and Toxicity Management:

Treatment can continue as monotherapy with either drugs if toxicity occurs that requires one drug to be discontinued, this is unlicensed.

Axitinib dose escalation/de-escalation

If the starting dose of 5mg twice daily is well tolerated for at least 2 consecutive weeks

- No adverse effects > grade 2
- Blood pressure < 150/90mmHg
- Not receiving anti-hypertensive treatment

Then the axitinib dose may be increased to 7mg twice daily.
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.

Axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily if not tolerated.

Avelumab dose escalation/de-escalation

Dosing delay or discontinuation may be required based on individual safety and tolerability.

Haematological toxicity:

For combination treatment and single agent Axitinib

Proceed on day 1 if-

ANC ≥ 1.5 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 1.4 x 10^9/L	Plt ≤ 99 x 10^9/L

For combination treatment
Proceed on day 15 if-

ANC ≥ 1.5 x 10^9/L	Plt ≥ 75 x 10^9/L

Omit on day 15 if-

ANC ≤ 1.4 x 10^9/L	Plt ≤ 74 x 10^9/L

On day 15 of the cycle if blood results do not meet the above levels the patient will miss that dose and proceed to the next cycle.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

For single agent Avelumab

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC clinical network immunotherapy acute oncology guidelines.

Proceed on day 1 if:-

Platelets	Neutrophils	Creatinine Clearance	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≥30 mL/min	<3 x ULN*	<5 x ULN	<5 x ULN	Within range or no change from base line

* ULN = upper limit of normal

The dose should be omitted if appropriate. Inform consultant if there has been an increase in liver function test from previous results.

Non- Haematological toxicity:

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

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 If persistent (greater than 5 days), corticosteroid therapy followed by a taper should be considered. Re-challenge with avelumab after recovery should be considered.
	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
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, pancreatitis, 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-mediate adverse reactions lasting 12 weeks or longer	Permanently discontinue

Hepatitis: Treatment modifications for avelumab and axitinib

If ALT or AST ≥ 3 times ULN but < 5 times ULN or total bilirubin ≥ 1.5 times ULN but < 3 times ULN, both avelumab and axitinib should be withheld until these adverse reactions recover to Grades 0-1.

If persistent (greater than 5 days), corticosteroid therapy (prednisone or equivalent) followed by a taper should be considered. Re-challenge with avelumab or axitinib or sequential re-challenge with both avelumab and axitinib after recovery should be considered. Dose reduction according to the axitinib product information should be considered if re-challenging with axitinib.

If ALT or AST ≥ 5 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN or total bilirubin ≥ 3 times ULN, both avelumab and axitinib should be permanently discontinued and corticosteroid therapy should be considered.

Axitinib	
Hypertension	Patients should be screened for hypertension and controlled as appropriate. During treatment, patients should be monitored for hypertension and treated as needed with anti-hypertensive therapy according to NICE guidelines. The aim is to achieve a blood pressure below 140/90. *Systolic 140-150 mmHg or Diastolic <90 mmHg:* -Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary. *Systolic 150-160mmHg or Diastolic 90-100mmgh:* -Continue treatment at same dose. -Repeat BP at GP, treatment needed if remained elevated or higher. -Continue with vigilant BP monitoring until BP <140/90mmHg. *Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart):* -Continue treatment at same dose -Instigate BP treatment, to be reviewed at GP within 5 days. -Continue with vigilant BP monitoring until BP <140/90mmHg. *Severe hypertension (>200mmHg systolic or >110mmHg diastolic)* Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment at reduced dose may be resumed once hypertension is appropriately controlled. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice – use NICE Clinical Guideline CG 127 – Hypertension in adults diagnosis and management: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE Verapamil and diltiazem should be avoided due to their inhibition of CYP3A4 enzymes.

	If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension.
Gastro-intestinal disorders	**Diarrhoea:** Grade 1 and 2 can be managed with supportive measures at home and with the use of anti-diarrhoea medication such as Loperamide 2mg after each stool if necessary. No treatment-break or dose changes required if symptom well controlled. Grades 3 and 4 will need treatment interruption until improvement to Grade 1 or less. 1 step dose reduction is required when restarted. Advise the patient to avoid any exacerbating foods and to eat small high carbohydrate meals. Also to drink plenty of water and to record the daily stool frequency. Also to drink plenty of water and to record their daily stool frequency. **Severe presentation** may need admission if associated with any of the following: nausea/vomiting, cramping, fever, sepsis, neutropenia or dehydration. **Nausea:** Domperidone is usually satisfactory. Nausea often settles with habituation to the drug. Administration of Sunitinib just before bedtime can help ameliorate this side-effect.

*Please refer to the renal TKI toxicity protocol for more information

References:

EMA. Inlyta Available from: https://www.medicines.org.uk/emc/product/4325/smpc#UNDESIRABLE_EFFECTS

Ema. Bavenico. Available from: https://www.medicines.org.uk/emc/product/8453

MHRA. Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/816840/Avelumab_EAMS_-_TP_for_HCPs_-_Final.pdf

NICE TA (TA645) Avelumab with axitinib for untreated advanced renal cell carcinoma. Published date: 02 September 2020.