

Chemotherapy Protocol

RENAL CELL

AVELUMAB-AXITINIB

Regimen

- Renal Cell - Avelumab-Axitinib

Indication

- Unresectable locally advanced or metastatic renal cell carcinoma (RCC) which has either a clear cell component or is one of the types of RCC as indicated below;
 - RCC with a clear cell component
 - Papillary RCC
 - Chromophobe RCC
 - Collecting duct RCC (Bellini collecting duct RCC)
 - Medullary RCC
 - Mucinous tubular and spindle cell RCC
 - Multilocular cystic RCC
 - XP11 translocation RCC

And the risk status as assessed by the International Metastatic RCC Database Consortium (IMDC) system which scores 1 point for each of the following 6 factors;

- less than 1 year from the time of initial diagnosis of RCC to now
- Karnofsky performance status of less than 80%
- haemoglobin level is less than the lower limit of normal
- corrected calcium level is greater than 2.5mmol/L
- platelet count is greater than the upper limit of normal
- neutrophil count is greater than the upper limit of normal

A score of 0 indicates good risk disease, 1-2 indicates intermediate risk and a score of 3-6 denotes poor risk.

- The patient is either completely treatment naïve for systemic therapy for RCC or if the patient has received prior systemic therapy in the context of adjuvant/neoadjuvant therapy, then such treatment was completed 12 months or more previously or the patient was entered into the EAMS scheme for avelumab plus axitinib.
- the patient has no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control.
- the patient is to be treated until loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner. There is no stopping rule as to the maximum treatment duration of avelumab plus axitinib in this indication. 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. Treatment breaks of up to 12 weeks beyond the expected 4-weekly cycle length are allowed but solely to allow any toxicities to settle.

- a formal medical review to assess the tolerability of treatment with avelumab and axitinib will be scheduled to occur at least by the start of the 3rd 4-weekly cycle of treatment and thereafter on a regular basis.
- if the disease progresses on the avelumab and axitinib combination and further systemic therapy is appropriate, the next line of treatment will be chosen from those options which are routinely commissioned ie for the next line of systemic therapy, there will be use of one choice of the following (mainly incorporating TKI options which have multiple modes of action [so-called 'dirty' TKIs]): the currently commissioned 2nd line options of cabozantinib or lenvatinib plus everolimus or everolimus monotherapy or the currently commissioned 1st line options of sunitinib (still on label as 2nd line treatment) or pazopanib (off label as 2nd line treatment).
- WHO performance status 0,1, 2

[Toxicity](#)

Drug	Adverse Effect
Axitinib	Hypertension, diarrhea, hypothyroidism, fatigue, skin/hair colour changes, palmar-plantar erythrodysesthesia, taste disturbances, oedema, epistaxis, mucositis
Avelumab	infusion related reactions, skin rashes, hepatitis, colitis, thyroid disorders, hypophysitis, nephritis, pneumonitis

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

[Monitoring](#)

Drugs

- FBCs, LFTs, U&Es, glucose and cortisol prior to days 1 and 15 for the first three cycles then prior to day 1 thereafter
- Blood pressure weekly for the first 4 weeks then every 4 weeks
- Thyroid function tests prior to starting treatment and then before each administration (cycle) or when clinically indicated (at least every 12 weeks)
- Urine assessment for proteinuria at baseline then every 12 weeks
- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured in patients with a history of cardiac problems or in the elderly. Repeat every three to six months as clinically indicated.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for SACT that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

For axitinib dose modifications should occur in incremental steps and are applied based on individual safety and tolerability. Both dose escalation from a starting dose of 5mg, and dose reductions should be considered. For example 5mg twice a day to 3mg twice a day to 2mg twice a day.

Avelumab belongs to the immunotherapy class of cancer treatments. Autoimmune toxicities are most frequently noted and can be life threatening. If autoimmune toxicities occur delaying treatment should be considered while investigations or treatments are organised. Some, but not all, toxicities mandate cessation of treatment. Please seek guidance from relevant site specific specialist teams or oncologists / haematologists with experience of prescribing these agents. Avelumab dose are delayed rather than reduced.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Avelumab dose is not generally reduced for haematological toxicity.

Prior to cycle 1 the following criteria should be met;

Criteria	Eligible Level
Neutrophil	Greater than or equal to $1 \times 10^9/L$
Platelets	Greater than or equal to $75 \times 10^9/L$

Thereafter;

Neutrophils (x10 ⁹ /L)	Dose Modifications
1 or greater	100%
less than 1	Delay until recovery to 1x10 ⁹ /L or greater. If recovery occurs within 7 days then continue with the last dose dose. If the recovery takes longer than 7 days then reduce the dose as described above.
Platelets (x10 ⁹ /L)	Dose Modifications
75 or greater	100%
Less than 75	Delay until recovery to 75x10 ⁹ /L or greater. If the recovery occurs within 7 days then continue with full dose. If recovery takes longer than 7 days then reduce the dose as described above.

Hepatic Impairment

Drug	Child Pugh Class	Starting Dose
Axitinib	A	5mg twice a day
	B	2mg twice a day
	C	No information

Avelumab, there is no dose adjustment is required in mild hepatic impairment. There is insufficient data from patients with moderate or severe hepatic impairment (bilirubin \geq 1.5 x ULN) for dosing recommendations.

See hepatitis section below for further information

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Axitinib	15 or less	No information

Avelumab, there is no dose adjustment is required in mild or moderate renal impairment. There is insufficient data from patients with severe renal impairment (CrCl less than 30ml/min) for dosing recommendations.

See nephritis section in table below for further information

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Overlapping Toxicity

Gastro-intestinal

Gastro-intestinal immune reactions include diarrhoea, increased frequency of bowel movements, abdominal pain or haematochezia, with or without fever. Diarrhoea also occurs with axitinib therapy. Patients should be advised to limit consumption of high fibre or spicy foods, caffeine, alcohol and dairy products. Laxatives should be avoided. For a NCI-CTC grade 1 diarrhoea continue treatment at the same dose and attempt dietary and dehydration management. Anti-diarrhoeal medicines, such as loperamide, may be necessary. For a NCI-CTC grade 2 or above adverse reaction stop both the avelumab and axitinib. Treatment may be re-started with a dose reduction of one dose level of axitinib in the first instance.

Diarrhoea or colitis occurring after initiation of avelumab must be promptly evaluated to exclude infectious or other alternate causes. Immune-related colitis is often associated with evidence of mucosal inflammation, with or without ulcerations and lymphocytic and neutrophilic infiltration.

For a NCI-CTC grade 2 – 3 colitis withhold both the avelumab and axitinib and administer corticosteroids. Upon improvement to NCI-CTC grade 1 colitis begin to taper the corticosteroid over a period of one month. Treatment may be re-started when the colitis remains at NCI-CTC grade 1 following corticosteroid taper.

The avelumab should be permanently discontinued when the colitis does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or any NCI-CTC grade 3 or above reaction.

Endocrine

Both hyper and hypothyroidism can occur and should be managed according to standard medical practice. There is no need to discontinue or dose reduce the axitinib or avelumab.

Hepatitis

Liver function should be monitored closely as there is a 9% incidence of NCI-CTC grade 3/4 raised transaminases and an increased incidence of immune-related hepatitis (6.3%) with this regimen.

If the ALT or AST is greater than or equal to 3 times ULN but less than 5 times ULN or total bilirubin is greater than or equal to 1.5 times ULN but less than 3 times ULN, both avelumab and axitinib should be withheld until these adverse reactions recover to NCI-CTC grades 0-1. If persistent (greater than 5 days), corticosteroid therapy with prednisone or equivalent followed by a taper should be considered. Upon improvement to NCI-CTC grade 1 hepatic injury begin to taper the corticosteroid over a period of one month. Both agents may be re-started when the liver function remains at NCI-CTC grade 1 following corticosteroid taper.

If ALT or AST is greater than or equal to 5 times ULN or greater than 3 times ULN with concurrent total bilirubin greater than or equal to 2 times ULN or total bilirubin greater than or equal to 3 times ULN, both avelumab and axitinib should be permanently discontinued and corticosteroid therapy should be considered.

The avelumab should be permanently discontinued when the hepatic injury does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid

dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or any NCI-CTC grade 3 or above reaction.

Avelumab should be permanently discontinued in the first instance when hepatitis develops that is associated with an AST / ALT equal to or greater than 5xULN, an increase in AST / ALT of 50% or greater relative to baseline and that lasts at least one week in patients with liver metastasis who begin treatment with moderate (grade 2) elevation of AST / ALT or where the bilirubin is greater than 3xULN.

After recovery from any NCI-CTC grade 2 hepatitis, consider sequential rechallenge with axitinib. Dose reduction of axitinib should be considered if rechallenging.

Skin

Serious skin reactions include dermatitis exfoliative, erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis. Avelumab can also be associated with pruritus, rash, (generalized and maculo-papular) and vitiligo. All attempts should be made to rule out other causes such as metastatic disease, infection or allergic dermatitis.

For NCI-CTC grade 1-2 skin reactions try symptomatic treatments such as topical corticosteroids or urea-containing creams in combination with oral antipruritics. Avelumab can continue.

For NCI-CTC grade 3 or above events withhold the avelumab and consider a dermatology referral. Treatment with systemic corticosteroids such as prednisolone 1mg/kg each day may be necessary. When symptoms improve to NCI-CTC grade 1 or less then steroid taper should be started and continued over no less than 4 weeks.

Palmar-plantar erythrodysesthesia can occur with axitinib. Patients should be advised to apply moisturiser to their hands and feet regularly throughout treatment, and to minimise activities that put pressure on feet or hands. Refer to a chiropodist if appropriate.

A NCI-CTC grade 1 reaction should be treated symptomatically. There is no need to interrupt therapy with axitinib or reduce the dose. For a NCI-CTC grade 2 effect delay treatment with axitinib until it resolves to at least NCI-CTC grade 1. The axitinib may be re-started with a dose reduction. The development of palmar-plantar erythrodysesthesia at NCI-CTC grade 3 should result in treatment being delayed until it resolves to NCI-CTC grade 1. The axitinib can be re-started with a reduced dose.

Axitinib may adversely affect the wound healing process. Stop axitinib at least 24 hours prior to scheduled surgery. The decision to resume axitinib after surgery should be based on clinical judgement of adequate wound healing.

Avelumab

Avelumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity, likely to be related to its pharmacology.

Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. Most occur during treatment, however, onset months after the last dose has been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and pembrolizumab-related. Early diagnosis and appropriate management are essential to minimise life threatening complications.

Treatment-related adverse reaction	Severity (NCI-CTC)	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
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 myositis, hypopituitarism, uveitis, Guillain-Barré)	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

syndrome)	For any of the following: <ul style="list-style-type: none"> • 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
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Axitinib

Cardiovascular

Hypertension should be treated initially as per the NICE guidelines⁽¹⁾. For persistently high blood pressure of more than 140/90mmHg despite standard hypertensive therapy, reduce the axitinib dose and continue to monitor. If hypertension persists discontinue the axitinib.

Dysphonia

Dysphonia includes sensation of lump in throat, difficulty swallowing, sore throat, hoarse voice and chronic throat clearing. This can be intermittent, but usually resolves after a 1-2 days of treatment interruption

Proteinuria

For patients who develop moderate to severe proteinuria (greater than or equal to 2 on dipstick, or greater than 1g/24 hours), reduce the axitinib dose or temporarily interrupt axitinib. Axitinib should be discontinued if the patient develops nephrotic syndrome

Regimen

28 day cycle until disease progression or unacceptable toxicity occurs (12 cycles will be set in ARIA)

Patients who tolerate the starting dose of axitinib 5mg twice a day with no adverse effects greater than NCI-CTC grade 2 in severity for two consecutive weeks may have the dose increased to 7mg twice a day unless the patient;

1. has blood pressure greater than 150/90 mmHg
2. is receiving antihypertensive medication

Patients who tolerate the dose of 7mg twice a day may have their dose increased to a maximum of 10mg twice a day following the same criteria.

This is the licensed dose escalation protocol. In practice it is unusual for this dose escalation to be tolerated. There will be a warning in ARIA to consider the dose escalation but the dose will be set in the system at the starting dose of 5mg twice a day.

Cycle 1

Drug	Dose	Days	Administration
Avelumab	800mg	1 and 15	Sodium chloride 0.9% 250mL over 60 minutes
Axitinib	5mg twice a day	1-14 incl.	Oral
	7mg twice a day (see above)	15-28 incl.	Oral

Cycle 2 Onwards

Drug	Dose	Days	Administration
Avelumab	800mg	1 and 15	Sodium chloride 0.9% 250mL over 60 minutes
Axitinib	10mg twice a day (see above)	1-28 incl.	Oral

[Dose Information](#)

- Axitinib is available as 1mg, 3mg, 5mg and 7mg tablets

[Administration Information](#)

- Swallow axitinib whole approximately 12 hours apart. Do not chew or crush
- Administer avelumab via a sterile, non-pyrogenic 0.2 micron in-line filter

[Additional Therapy](#)

- Prior to treatment with avelumab
 - chlorphenamine 10mg intravenous
 - paracetamol 1000mg oral

If the 4th infusion is completed without an infusion-related reaction, no pre-med before subsequent doses is routinely required.
- Mouthwashes according to local or national policy on the treatment of mucositis.
- Loperamide 4mg oral after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).

[Additional Information](#)

- The National Patient Safety Alert on oral SACT (NPSA/2008/RRR001) must be followed in relation to axitinib.

- It must be made clear to all staff, including those in the community, that axitinib should only be prescribed under the supervision of an oncologist.
- Axitinib is associated with drug interactions
- Patients should be given an avelumab alert card and be advised to carry this card at all times and show it to any healthcare professional with whom they come into contact for a medical visit

References

1. T K Choueiri , R J Motzer, B I Rini. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Annal Oncol* (2020);31(8):1030-1039

REGIMEN SUMMARY

Avelumab-Axitinib

Cycle 1 – Day 1 and 15

1. Chlorphenamine 10mg intravenous
2. Paracetamol 1000mg oral
Administration Instructions
The maximum daily dose of paracetamol is 4000mg per 24 hours. Please check if the patient has taken paracetamol
3. Avelumab 800mg intravenous infusion in 250ml of sodium chloride 0.9% over 60 minutes
Administration Instructions
Administer via a sterile, non-pyrogenic 0.2 micron in-line filter

Take Home Medicines (Day 1)

4. Axitinib 5mg twice a day for 14 days oral
Administration Instructions
Oral SACT
Please note this dose has **not** been automatically escalated by ARIA as in practice patients rarely tolerate dose escalation; please check the dose is appropriate for the patient.

Patients who tolerate the starting dose of axitinib 5mg twice a day for 14 days with no adverse effects greater than NCI-CTC grade 2 in severity for two consecutive weeks may have the dose increased to 7mg twice a day for 14 days unless the patient ;

1. has blood pressure greater than 150/90 mmHg
2. is receiving antihypertensive medication

Patients who tolerate the dose of 7mg twice a day for 14 days may have their dose increased to a maximum of 10mg twice a day following the same criteria

Take Home Medicines (Day 15)

5. Warning – Consider Axitinib Dose Escalation
Administration Instructions
Please note this dose has **not** been automatically escalated by ARIA as in practice patients rarely tolerate dose escalation; please check the dose is appropriate for the patient.

Patients who tolerate the starting dose of axitinib 5mg twice a day for 14 days with no adverse effects greater than NCI-CTC grade 2 in severity for two consecutive weeks may have the dose increased to 7mg twice a day for 14 days unless the patient;

1. has blood pressure greater than 150/90 mmHg
2. is receiving antihypertensive medication

Patients who tolerate the dose of 7mg twice a day for 14 days may have their dose increased to a maximum of 10mg twice a day following the same criteria

6. Axitinib 5mg twice a day for 14 days oral
Administration Instructions
Oral SACT
Please note this dose has **not** been automatically escalated by ARIA as in practice patients rarely tolerate dose escalation; please check the dose is appropriate for the patient.

Patients who tolerate the starting dose of axitinib 5mg twice a day for 14 days with no adverse effects greater than NCI-CTC grade 2 in severity for two consecutive weeks may have the dose increased to 7mg twice a day for 14 days unless the patient;

1. has blood pressure greater than 150/90 mmHg
2. is receiving antihypertensive medication

Patients who tolerate the dose of 7mg twice a day for 14 days may have their dose increased to a maximum of 10mg twice a day following the same criteria

Cycle 2 Day 1 and 15

7. Chlorphenamine 10mg intravenous

8. Paracetamol 1000mg oral

Administration Instructions

The maximum daily dose of paracetamol is 4000mg per 24 hours. Please check if the patient has taken paracetamol

10. Avelumab 800mg intravenous infusion in 250ml of sodium chloride 0.9% over 60 minutes

Administration Instructions

Administer via a sterile, non-pyrogenic 0.2 micron in-line filter

Take Home Medicines (Day 1)

11. Warning – Consider Axitinib Dose Escalation

Administration Instructions

Please note this dose has **not** been automatically escalated by ARIA as in practice patients rarely tolerate dose escalation; please check the dose is appropriate for the patient.

Patients who tolerate the starting dose of axitinib 5mg twice a day for 14 days with no adverse effects greater than NCI-CTC grade 2 in severity for two consecutive weeks may have the dose increased to 7mg twice a day for 14 days unless the patient;

1. has blood pressure greater than 150/90 mmHg
2. is receiving antihypertensive medication

Patients who tolerate the dose of 7mg twice a day for 14 days may have their dose increased to a maximum of 10mg twice a day following the same criteria

12. Axitinib 5mg twice a day for 28 days oral

Administration Instructions

Oral SACT

Please note this dose has **not** been automatically escalated by ARIA as in practice patients rarely tolerate dose escalation; please check the dose is appropriate for the patient.

Patients who tolerate the starting dose of axitinib 5mg twice a day for 14 days with no adverse effects greater than NCI-CTC grade 2 in severity for two consecutive weeks may have the dose increased to 7mg twice a day for 14 days unless the patient;

1. has blood pressure greater than 150/90 mmHg
2. is receiving antihypertensive medication

Patients who tolerate the dose of 7mg twice a day for 14 days may have their dose increased to a maximum of 10mg twice a day following the same criteria

Cycle 3 Onwards - Day 1 and 15

13. Warning - Check pre-medication

Administration Instructions

If the patient has had no previous infusion related reactions to avelumab the premedication given during the first four infusions can be omitted from infusion five onwards. If reactions have occurred consider re-prescribing the pre-medication.

14. Avelumab 800mg intravenous infusion in 250ml of sodium chloride 0.9% over 60 minutes

Administration Instructions

Administer via a sterile, non-pyrogenic 0.2 micron in-line filter

Take Home Medicines (Day 1)

15. Warning – Consider Axitinib Dose Escalation

Administration Instructions

Please note this dose has **not** been automatically escalated by ARIA as in practice patients rarely tolerate dose escalation; please check the dose is appropriate for the patient.

Patients who tolerate the starting dose of axitinib 5mg twice a day for 14 days with no adverse effects greater than NCI-CTC grade 2 in severity for two consecutive weeks may have the dose increased to 7mg twice a day for 14 days unless the patient;

1. has blood pressure greater than 150/90 mmHg
2. is receiving antihypertensive medication

Patients who tolerate the dose of 7mg twice a day for 14 days may have their dose increased to a maximum of 10mg twice a day following the same criteria

16. Axitinib 5mg twice a day for 28 days oral

Administration Instructions

Oral SACT

Please note this dose has **not** been automatically escalated by ARIA as in practice patients rarely tolerate dose escalation; please check the dose is appropriate for the patient.

Patients who tolerate the starting dose of axitinib 5mg twice a day for 14 days with no adverse effects greater than NCI-CTC grade 2 in severity for two consecutive weeks may have the dose increased to 7mg twice a day for 14 days unless the patient;

1. has blood pressure greater than 150/90 mmHg
2. is receiving antihypertensive medication

Patients who tolerate the dose of 7mg twice a day for 14 days may have their dose increased to a maximum of 10mg twice a day following the same criteria

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Nov 2020	None	Dr Deborah Wright Pharmacist	Dr Mathew Wheeler Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.