AVELUMAB AXITINIB (Bavencio, Inlyta)

INDICATION (ICD10) C64

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

For use in treatment-naïve patients with advanced renal cell carcinoma where the following criteria have been met:

2. Fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to checkpoint inhibitor treatments including pneumonitis, colitis, nephritis, endocrinopathies, hepatitis and other immune-related adverse reactions.
3. Unresectable locally advanced or metastatic renal cell carcinoma (RCC) which has either a clear cell component or is one of the types of RCC. RCC with a clear cell component or Papillary RCC or Chromophobe RCC or Collecting duct RCC (Bellini collecting duct RCC) or Medullary RCC or Mucinous tubular and spindle cell RCC or Multilocular cystic RCC or XP11 translocation RCC or Unclassified RCC
4. Risk status as assessed by the International Metastatic RCC Database Consortium (IMDC) system which scores 1 point for each of the following 6 factors – a score of 0 indicates good risk disease, a score of 1-2 indicates intermediate risk and a score of 3-6 denotes poor risk: The IMDC factors are:
- less than 1 year from time of initial diagnosis of RCC to now
- a Karnofsky performance status of <80%
- the haemoglobin level is less than the lower limit of normal
- the corrected calcium level is >2.5mmol/L
- the platelet count is greater than the upper limit of normal
- the absolute neutrophil count is greater than the upper limit of normal.

5. 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 previously or the patient was entered into the EAMS scheme for avelumab plus axitinib.
6. ECOG performance status of 0 or 1.
7. No symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control.
8. To be treated until loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner.Note: there is no stopping rule as to the maximum treatment duration of avelumab plus axitinib in this indication. Note: 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.
9. Avelumab and axitinib will otherwise be prescribed and administered as outlined in their respective Summary of Product Characteristics (SPCs).
10. 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.
11. Treatment breaks of up to 12 weeks beyond the expected 4-weekly cycle length are allowed but solely to allow any toxicities to settle.
12. 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.

REGIMEN

Day 1 Premedication 30 minutes prior to infusion (see concurrent medication):
Chlorphenamine 10mg IV bolus
Paracetamol 1000mg tablet
AVELUMAB 800mg in 250ml sodium chloride IV infusion over 60 minutes
Days 1 to 14 AXITINIB 5mg oral twice daily continuously

ADMINISTRATION

Axitinib
Available as 1mg, 3mg, 5mg and 7mg tablets
Swallow whole with or without food.
Grapefruit and grapefruit juice should be avoided while on Axitinib.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 14 days
A medical review as to whether treatment with avelumab should continue or not will need to occur at least by the end of the first 8 weeks of treatment.
Avelumab is to be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment. 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.

ANTI-EMETICS

Minimal emetic risk

CONCURRENT MEDICATION REQUIRED

Avelumab	Ensure premedication give before avelumab for first 4 cycles, then if the fourth infusion is completed without an infusion-related reaction, premedication for subsequent doses should be administered at the discretion of the physician.
Axitinib	Loperamide cycle 1

EXTRAVASATION AND TYPE OF LINE / FILTERS

Avelumab - neutral

Use 0.2micron low-protein binding in-line filter.
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥75
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Avelumab	Immune related toxicities - pneumonitis, colitis or hepatitis etc
Axitinib	Diarrhoea Hand-foot syndrome Haemorrhage – increased risk of bleeding Hypertension Hypothyroidism Proteinurea Wound healing delayed

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Axitinib	Anticoagulants

DOSE MODIFICATIONS
When dose reduction is necessary, the axitinib dose may be reduced to 3mg twice daily and further to 2mg twice daily.

Haematological
Axitinib
Temporarily interrupt axitinib if any bleeding event requires medical intervention.

Non-haematological
Avelumab
Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline

Axitinib

Hypertension	Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension, despite use of antihypertensive 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. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension
Proteinuria	Moderate to severe proteinuria develops (≥2+ on dipstick, or >1g/24 hours), reduce dose or temporarily interrupt axitinib. Axitinib should be discontinued if the patient develops nephrotic syndrome.

Hepatic impairment
Avelumab
No dose adjustment is needed for patients with mild hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations.

Axitinib
Child-Pugh scores are based on ascites, encephalopathy, INR, albumin, total bilirubin

Mild hepatic impairment (Child-Pugh A)	No dose adjustment
Moderate hepatic impairment (Child-Pugh B)	A dose decrease is recommended, the starting dose should be reduced from 5mg bd to 2mg bd
Severe hepatic impairment (Child-Pugh C).	Not recommended

Renal impairment

Avelumab

No dose adjustment is needed for patients with mild or moderate renal impairment. There are insufficient data in patients with severe renal impairment for dosing recommendations.

Axitinib

No dose adjustment is required in renal impairment.

REFERENCES

1. D'Angelo, S et al; JAMA Oncol 2018; 4(9):e180077. doi:10.1001/jamaoncol.2018.0077