Chemotherapy Protocol

BLADDER CANCER

AVELUMAB (800mg)

Regimen

- Bladder Cancer - Avelumab

Indication

- Avelumab is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line treatment with gemcitabine in combination with either cisplatin or carboplatin. The patient must have completed at least 4 cycles and no more than 6 cycles of combination chemotherapy with gemcitabine plus cisplatin or carboplatin.

- The patient must have had a CT or MR scan after completing this chemotherapy and has been shown to have no evidence of progressive disease compared with the scans performed prior to chemotherapy and with any scans whilst on chemotherapy. in or gemcitabine plus carboplatin.

- The patient must commence treatment with avelumab within 4 to 10 weeks of receiving the last dose of chemotherapy and that maintenance treatment with avelumab monotherapy will continue until disease progression or symptomatic deterioration or unacceptable toxicity or withdrawal of patient consent, whichever occurs first.

- The patient has no symptomatically active brain metastases or leptomeningeal metastases

- The patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.

- A formal medical review as to how treatment with avelumab is being tolerated and whether treatment with avelumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

- That where a treatment break of more than 12 weeks beyond the expected 2-weekly cycle length is needed, a treatment break form to restart treatment will be completed.

- WHO Performance status 0, 1

Toxicity

Drug	Adverse Effect
Avelumab	Nephritis, colitis, thyroid disorders, hypophysitis, infusion related reactions, hepatitis, pneumonitis

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

Monitoring

Drugs

- FBCs, LFTs and U&Es prior to day 1 for six cycles and then, if stable, every four weeks thereafter
- Thyroid function tests prior to staring treatment and then every four weeks for twelve weeks or when clinically indicated (at least 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.

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.

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. Treatment is delayed rather than reduced.

Prior to cycle 1 the following criteria should be met;

Criteria	Eligible Level
Neutrophil	Greater than or equal to $1x10^9$/L
Platelets	Greater than or equal to $100x10^9$/L

Hepatic Impairment

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 ≥ 1.5 x ULN) for dosing recommendations.

Renal Impairment

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.

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.

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 the avelumab.

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 the avelumab 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

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, avelumabshould 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. Avelumab 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, the avelumab 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.

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.

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: • 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

Regimen

14 day cycle until disease progression or unacceptable toxicity occurs (26 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Avelumab	800mg	1	Sodium chloride 0.9% 250ml over 60 minutes

Administration Information

- 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

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. MHRA. Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals. Accessed 29/09/2020 at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/913666/Avelumab_Treatment_protocol_for_healthcare_professionals.pdf

REGIMEN SUMMARY

Avelumab (800mg)

Cycle 1, 2, 3, 4

1. Chlorphenamine 10mg intravenous
   Administration Instructions
   Administer 30 minutes prior to avelumab

2. Paracetamol 1000mg oral
   Administration Instructions
   Administer 30 minutes prior to avelumab
   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

Cycle 5 Onwards

4. 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 cycles can be omitted from cycle five onwards. If reactions have occurred consider re-prescribing the pre-medication.

5. 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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Nov 2020	None	Dr Deborah Wright Pharmacist	Dr Caroline Chau 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.